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THE BACTERIOLOGICAL DIAGNOSIS OF SEVERE CLOSTRIDIUM WELCHII INFECTION FOLLOWING ABORTION.¹

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DURING the last eighteen months a study has been made of abortifol infections due to *Clostridium welchii*. In this hospital the majority of severe and fatal abortifol infections caused by this organism are characterized by jaundice and gross blood destruction; cases of metastatic gas gangrene also occur, but are rare. The main purpose of the investigations recorded in this paper was to determine a method for the rapid bacteriological diagnosis of these types of severe infection.

The first stage of the work was to ascertain how often *Clostridium welchii* could be cultivated from the vagina, and to determine whether the presence of this organism indicated that the patient was infected with it.

The Frequency of *Clostridium Welchii* in the Vagina.

Two methods were used for the cultivation of *Clostridium welchii* from the vagina. (a) The vaginal swab was plated directly on blood agar and the plates were incubated in a McIntosh and Fildes anaerobic jar. (b) The vaginal swab was used to inoculate a tube of Wright's broth⁽¹⁾ (12 cubic centimetres) containing cooked minced veal.

¹Work done with the aid of a grant from the National Health and Medical Research Council.

In 100 cases both types of culture media were inoculated from the same swab and both proved equally satisfactory for the detection of *Clostridium welchii*. The cultures in broth have the advantage that they can be made at any time with a minimum of trouble, since the medium keeps for several weeks at room temperature, and, when inoculated, does not need to be incubated in the anaerobic jar.

For the purpose of this investigation an organism was regarded as *Clostridium welchii* if its morphology was typical of that organism, if it failed to grow on surface plates under aerobic conditions, and if it gave typical stormy fermentation in milk. The appearance of the growth on blood agar plates incubated anaerobically was so variable, as to both the colony form and the occurrence of haemolysis, that it could not always be used as a criterion of identification. In some instances further proof of the nature of the organism was obtained by animal inoculation.

Vaginal cultures in broth were made as a routine measure from all patients who had had an abortion, both with and without signs of sepsis, on their admission to hospital. During the fourteen months from February 1, 1939, to April 1, 1940, 1,480 such cultures were examined and 394 (or 27%) showed *Clostridium welchii*. This high proportion of positive findings was very different from that observed in puerperal cases. During this same period only nine (or 3.5%) of 260 vaginal cultures from puerperal patients yielded *Clostridium welchii*.

The figures for the puerperal cases are of the same order as those reported by Bysshe (1938),⁽²⁾ who found that of 203 vaginal cultures taken during the puerperium, 10 yielded *Clostridium welchii*. Bysshe also recovered this organism from the vagina in cases of abortion, but he

did not record the precise figures. Falls (1933)⁽⁵⁾ found *Clostridium welchii* in the vagina in five out of 22 cases of incomplete abortion.

The Significance of *Clostridium Welchii* in the Vagina.

An analysis of the case histories showed that 169 of the 394 women harbouring *Clostridium welchii* in the vagina were without symptoms of infection. Of the remaining 225, 133 were febrile for one, two or three days, and 92 showed signs of more serious infection.

This last group included 11 women who died as the result of infection with *Clostridium welchii*, two who died from a mixed infection due to *Clostridium welchii* and *Clostridium septicum*, and two who were very gravely ill as the result of infection with *Clostridium welchii*.

No case of severe infection due to *Clostridium welchii* was observed in which the infecting organism was not detected in the vaginal culture.

The number of *Clostridia welchii* present in the vaginal culture was not significant. In 297 instances there were many such bacilli in the vaginal culture, and 174 of these patients showed symptoms of sepsis, while of the 97 patients from whose vaginal swab only small numbers of *Clostridia welchii* were obtained, 51 showed similar symptoms. In two of the fatal *Clostridium welchii* infections only small numbers of the infecting organism were detected in the vaginal culture.

While the absence of *Clostridium welchii* from the vaginal culture is strong evidence against the possibility of a severe infection, the converse is not true. The presence of *Clostridium welchii* in the vagina cannot in itself be regarded as diagnostic of infection.

The next step was to assess in what percentage of abortions the presence of *Clostridium welchii* in the vagina was associated with the presence of this organism in the uterine contents.

The Frequency and Significance of *Clostridium Welchii* in the Uterine Contents.

In 241 of the cases of incomplete abortion cultures were made from both the vaginal swab and the placental tissue obtained by curettage. Only five of these patients showed definite symptoms of infection at the time the curettage was performed.

In 37 cases *Clostridium welchii* was obtained from both sites, in 29 from the vagina only, and in four from the placental tissue only.

Although the figures here are not so large as one might wish, they do indicate that in a large proportion of the abortions in which *Clostridium welchii* is recovered from the vaginal swab, the same organism is present in the uterus.

In regard to the significance of the detection of *Clostridium welchii* in the uterine contents, a study of the histories showed that of these 41 patients, 17 were without symptoms of infection, 18 showed a slight degree of fever for one, two or three days, and six were classified as "septic cases". Of the last six, not one showed signs of severe infection.

It is difficult to escape the conclusion that the detection of *Clostridium welchii* in the uterine contents is of no greater diagnostic value than the cultivation of this organism from the vagina.

Such a finding was not unexpected in view of the cases reported by Wrigley (1930)⁽⁶⁾ and Falls (1933).⁽⁵⁾ Both these writers described cases in which the foetus and placenta were heavily infected with *Clostridium welchii*, yet the mother was not gravely ill. In one of Falls's abortifacient cases, in which the foetus was distended with gas due to the activity of *Clostridium welchii*, the woman showed no symptoms of infection.

The Value of Cultures from the Urine.

Previous experience in this hospital had shown that *Clostridium welchii* could usually be cultivated from the urine in cases of severe infection due to this organism.

During the course of the present investigation cultures were made from the urine of 87 women who harboured *Clostridium welchii* in the vagina. In 12 out of 14 severe or fatal cases of *Clostridium welchii* infection this organism was present in the urine; but *Clostridium welchii* was present in the urine also in 18 out of 35 septic cases in which the clinical signs were not thought to be due to a severe *Clostridium welchii* infection, and in 8 out of 38 cases in which symptoms of infection were mild or absent.

The different proportion of patients yielding *Clostridium welchii* from the urine in these three groups did not suggest that the presence of this organism was due to contamination during catheterization. Furthermore, among more than 200 specimens of urine from abortifacient and puerperal patients who did not harbour *Clostridium welchii* in the vagina, and from patients with suspected urinary infection during pregnancy, *Clostridium welchii* was recovered only once, although the method of cultivation was the same in all instances.

While the isolation of *Clostridium welchii* from the urine probably indicates that this organism has at some time found its way into the blood stream, it cannot be regarded as an indication of a severe infection. Even the cultivation of this organism from the blood cannot invariably be regarded as diagnostic of a severe infection. Both Bingold (1923)⁽⁷⁾ and Hill (1936)⁽⁸⁾ mention instances in which *Clostridium welchii* was cultivated from the blood of women who were not seriously ill.

How, then, are we to make a bacteriological diagnosis of a severe *Clostridium welchii* infection? Why in one woman does the introduction of *Clostridium welchii* into the uterus cause a rapid and fatal infection and in another woman no symptoms at all?

The explanation of this extraordinary variability must be due either to wide variation in the susceptibility to infection of these women or to the differing pathogenic powers of the bacteria. It is this latter possibility which has been studied, since it was thought that if this were so the detection in the vagina of strains likely to cause severe infection would be a valuable diagnostic aid.

The Characteristics of the Strains of *Clostridium Welchii* Isolated in Abortifacient Cases.

With an organism such as *Clostridium welchii* one must consider both the toxin production of the strain and its ability to spread beyond the initial site of infection.

Non-toxic variants of *Clostridium welchii* are known, and it was at first thought that the strains obtained from the uterine contents of patients who did not show symptoms of severe infection might fall within this category. Six strains isolated from placental tissue of patients who showed no symptoms of infection, and six similar strains from women who were only mildly ill, were tested for pathogenicity for guinea-pigs. The strains were grown for eighteen hours in meat broth similar to that used for the vaginal culture. When 0.1 cubic centimetre of the culture was injected intramuscularly, all but two strains caused death. The two strains which failed to kill guinea-pigs were from women who showed no clinical signs of infection.

These results did not suggest that the study of the pathogenicity for guinea-pigs would explain the apparent differences in human virulence. This, however, must not be taken to mean that differences in the toxin production of different strains are without importance in the determination of the clinical picture. The work of Ipsen and Davoli (1939)⁽⁹⁾ showing the antigenic differences of toxins produced with various strains and media makes this appear very probable. Such assays, however, are usually beyond the scope of hospital laboratories.

There remains the other line of investigation, the study of the characteristics of the bacterium itself, especially of those properties which may be related to its power to spread beyond the initial site of infection.

It is well established that *Clostridium welchii* is subject to great variation in colony form. The two generally recognized types, the smooth and the rough, have been described for this organism, and also a number of

apparently intermediate variants. For many species of bacteria it has been found that rough variants have lost (either entirely or in part) the virulence possessed by the normal smooth form. In those species which form capsules, mucoid variants may also occur, and such variants often possess maximum virulence. In general, mucoid variants have large capsules; the smooth may or may not be capsulated, while the rough are very seldom capsulated.

The large number of colony forms of *Clostridium welchii* intermediate between rough and smooth, the occurrence of mucoid rough variants as well as mucoid variants of the smooth type, and the rapid transformation from rough to smooth that may occur when an animal is inoculated with a rough variant culture, have apparently led different workers to attribute different properties to various types of colony. Buchaly (1931)⁽⁹⁾ found the smooth variant more virulent than the rough, as did also Orr *et alii* (1933).⁽¹⁰⁾ McGaughey (1933)⁽¹¹⁾ described two rough variants, one of which produced a more powerful toxin than the normal smooth variant. But on his own description this variant was unlike a typical rough strain, since the surface of the colonies was smooth and the cultures showed capsulated organisms. Roe (1934)⁽¹²⁾ held that strains giving rough colonies were more virulent than the smooth; but he stated that the rough variants were unstable.

In addition to the colony variations, morphological differences have been observed. Rough strains show chains of bacilli and filamentous forms and are usually not capsulated. Orr *et alii* (1933)⁽¹⁰⁾ and McGaughey (1933)⁽¹¹⁾ found the smooth type capsulated, but Stevens (1935)⁽¹³⁾ held that only the mucoid variants formed capsules. Stevens, however, described his smooth colonies as having a finely granular and wavy surface, which suggests that he was not using the term in the same sense as the other workers mentioned.

I have found no record of any attempt to correlate the variation of *Clostridium welchii* with differences in the clinical picture of human infections. If the results in animals are applicable to human disease, one would expect that those strains causing grave symptoms, especially of a character consistent with infection by a highly invasive bacterium, would be smooth variants. Rough variants, if present in the uterus after an abortion, would be unlikely to set up a serious infection.

In order to test this hypothesis the growth characteristics and morphology of a large number of strains have been studied. The most significant characteristics from the standpoint of human virulence appeared to be: (i) the appearance of the colonies on blood agar plates, (ii) the type of growth in a liquid medium consisting of equal parts of 1% neopeptone in water and normal horse serum, and (iii) the occurrence of capsulated forms in broth cultures.

Growth Characteristics and their Significance.

Colony Form.—Three types of blood agar plates were used in the preliminary tests—nutrient agar containing 10% of citrated horse blood, the horse blood agar plates used by Ward and Rudd⁽¹⁴⁾ for the study of the hæmolytic streptococci, and plates made from Huntton's⁽¹⁵⁾ hormone agar and defibrinated rabbit's blood, as recommended by Orr *et alii*.⁽¹⁰⁾ The last mentioned medium gave the most consistent results and was used to compare the strains from 110 abortion cases. The plates were incubated in anaerobic jars containing calcium chloride in order to control the amount of moisture. In those cases in which more than one culture of *Clostridium welchii* was obtained from the same patient, no differences were detected between the various strains. For this reason the results with only one strain from each patient are recorded.

The strains could be divided into four groups: (i) 20 strains which gave smooth raised colonies with an unbroken edge; the colonies produced by three of these strains were mucoid; (ii) 24 strains which gave raised colonies, the surface of which was smooth except for slight granularity at the periphery; (iii) 58 strains which gave slightly raised colonies with a dull or finely granular

surface and an uneven edge (two of these strains were mucoid); (iv) 8 strains which gave very flat colonies with a rough granular surface and very uneven edge. Strains belonging to the first group were regarded as smooth variants. Those of the second group appeared to be very closely related to the smooth variants in the same way as those of the third group were related to the typical rough variants which composed the fourth group. For the sake of brevity I have called the strains belonging to the second group intermediate smooth variants, and those of the third group intermediate rough variants.

Among these 110 strains there were 13 from very severe infections. (The strains from the two patients who were also infected with *Vibrio septique* were not included.) All but two of these 13 strains were smooth variants as judged by colony form. The remaining two strains were unstable; but the most usual variant produced was of the intermediate smooth type. It may be significant that the 11 typically smooth strains were from cases in which jaundice and gross blood destruction were the outstanding clinical signs. This is in keeping with the finding of Orr *et alii*⁽¹⁰⁾ that the toxin formed by smooth variants, when given intravenously in a standardized dose to rabbits, produced a greater degree of anæmia than the same dose of toxin from rough strains. The two unstable strains were both from fatal cases; but the first was of metastatic gas gangrene and the second case was not associated with jaundice or metastatic lesions. These two unstable strains were unlike any of the other strains observed during this investigation. With 16 strains isolated from the uterine contents of women who were either symptomless or only mildly ill, the results were very different from those obtained with the strains causing the fatal infections. Only two of these 16 were smooth variants. Five were intermediate smooth variants and the remaining nine intermediate rough variants.

Growth in Serum-Neopeptone-Water Mixture.

The majority of the strains of *Clostridium welchii*, when grown under anaerobic conditions in a mixture of equal parts of normal horse serum and 1% neopeptone¹ in water, formed a flocculent, granular or flaky deposit, usually with the supernatant fluid unclouded. Some of the strains, however, gave an even clouding of the medium, and some produced a deposit which was not granular and which formed an even emulsion when shaken.

With some samples of horse serum the *Clostridium welchii* strains produced an opalescence in this mixture; but this was seldom apparent in less than twenty-four hours' incubation. To avoid possible confusion between diffuse growth and opalescence, it was found advisable to record the character of the growth in serum-neopeptone-water after not more than twenty four hours' incubation. This opalescence was evidently due to the toxin produced, since it was completely inhibited by *Clostridium welchii* antitoxin. The character of the growth was not appreciably affected by the addition of antitoxin to the medium. The production of opalescence appears to be a similar phenomenon to that described by Nagler (1939)⁽¹⁶⁾ as occurring in human serum, although this investigator stated that he had not observed such an effect with horse serum.

The character of the growth in serum-neopeptone-water showed some correspondence with surface colony form, and could also be partially correlated with human virulence. All but one of the 20 strains which on colony form appeared to be smooth variants, gave a non-granular growth in serum-neopeptone-water. Of the 24 intermediate smooth strains, 13 gave a non-granular type of growth. All of the rough variants and all but three of the 58 intermediate rough strains produced a coarse granular deposit. With the mucoid variants of the latter type the growth was stringy rather than granular, but it did not readily give an even emulsion when shaken.

As we pass from smooth variants to rough there is a corresponding increase in the tendency to produce a flocculent granular type of growth in serum-neopeptone-water.

¹ "Difco" brand.

All but three of the strains causing the fatal and severe infections behaved alike; they gave a non-granular growth, usually an even clouding of the medium. Two of the three strains which produced a granular growth were the unstable strains mentioned in the preceding section.

Of the 16 strains from the uterine contents of women who were symptomless or only mildly ill, five produced a non-granular growth and 11 gave a granular deposit.

It is possible that variation occurred with some of the strains during their isolation in pure culture, and that some of the cultural differences observed were due to such changes. Furthermore, in a few instances the strains had been kept in meat broth for as long as three months before the growth characteristics were studied. Marked changes, however, were probably not very common, for among 40 strains tested immediately after isolation and at intervals during the subsequent two to four months, only four showed considerable change.

After two and four months, respectively, of artificial cultivation, two strains which were initially smooth produced colonies on surface plates resembling those of intermediate rough variants and grew as a granular deposit in serum-neopeptone-water. Two intermediate rough variants became mucoid, but retained their original characteristics in other particulars.

Also the similarity of the different strains from the same patient, although such strains were often tested at different times, did not suggest that very much change occurred during the first few weeks of artificial cultivation.

Since the number of severe and fatal cases that have been so far studied is less than 20, it did not appear worth while to submit this material to statistical analysis. The results suggest that only certain cultural variants are able to cause severe infections. Strains which give typically smooth colonies on surface plates and produce a non-granular type of growth in serum-neopeptone-water appear to be the most likely to cause the infections characterized by jaundice and gross blood destruction.

Capsulation in Broth Cultures and its Diagnostic Significance.

While the recognition of those cultural variants known to cause severe infections is most important for proving the diagnosis of a severe *Clostridium welchii* infection and should be of value in assessing the efficacy of various therapeutic measures, cultural studies cannot be carried out sufficiently quickly to serve as a means of rapid bacteriological diagnosis in individual cases. The only practical method would be to detect differences in the primary cultures or in smears direct from the patient.

Since in general the smooth variants of *Clostridium welchii* are capsulated, while the rough strains are not, it seemed likely that the degree of capsulation occurring in the meat broth cultures made from the vaginal swab would serve to differentiate those variants which were associated with the severe infections. This contention has proved correct in many instances.

Smears made after twelve to twenty-four hours' incubation from 230 consecutive vaginal cultures which showed *Clostridium welchii* were stained by Richard Muir's method. The presence or absence of capsules and the relative length and breadth of the bacilli were noted.

On this basis the 230 strains fell into three groups. In the first group were 26 heavily capsulated strains, which usually showed short, stout, square-ended bacilli. The 64 strains of the second group were also capsulated, but not heavily so. The third group comprised 140 strains which showed very few capsulated bacilli; some smears showed no capsular material, and in many the bacilli were long and thin. Chains and filamentous forms were also seen.

The addition of blood or serum to the broth may cause a marked increase in capsulation. With some strains the addition of 0.1 cubic centimetre of blood to 15 cubic centimetres of broth gave rise to considerable increase in capsular material. Care should be taken in the inoculation of the meat broth from the vaginal swab that as little blood as possible is added to the medium. If a visible amount of blood is present in a vaginal culture which shows heavily or moderately heavily capsulated bacilli

resembling *Clostridium welchii*, a subculture in a fresh tube of broth is necessary.

Differences in the size, arrangement and capsulation of the various strains were also observed in the serum-neopeptone-water cultures. Smears at the end of twenty-four hours' incubation from strains which grew profusely or formed a readily emulsifiable non-granular deposit, showed large stout bacilli arranged either singly or in pairs. These bacilli were usually heavily capsulated and spores were not present. Smears from the granular type of growth showed bacilli which were thinner than those of the diffuse cultures and were arranged in masses or chains. Capsulation was very poor, and when chains occurred spore formation was observed. In some instances the chains appeared to be encased between faintly stained strands. This material stained less readily than the capsular substance of the diffuse-growing strains, and was possibly identical with the sheaths observed by Stevens¹² with rough variants.

The strains from 90 of the 230 vaginal cultures which were examined for capsule formation were also studied culturally. Of these 90, 18 were heavily capsulated in the broth cultures, 37 belonged to the second group on the basis of capsule formation, and 35 belonged to the group which showed little, if any, capsular material.

The relationship between capsulation in the primary broth culture, colony form on blood agar and growth in serum-neopeptone-water is given in Table I.

TABLE I.
Relationship between Capsulation and Growth Characteristics.

Capsulation in the Primary Broth Culture.	Colony Form.	Number of Strains.	Growth in Serum-neopeptone-water. ¹
Heavy.	Smooth	10	9 (7) non-granular. 1 (1) granular.
	Intermediate smooth	3	1 non-granular. 2 (2) granular.
	Intermediate rough ..	5	All granular.
Moderate.	Smooth	7	6 non-granular. 1 granular.
	Intermediate smooth	17	10 non-granular. 7 granular.
	Intermediate rough ..	13	1 non-granular. 12 granular.
	Smooth	1	Granular.
Slight or Absent.	Intermediate smooth	3	1 non-granular. 2 granular.
	Intermediate rough ..	28	All granular.
	Rough	3	All granular.

¹ The figures in parentheses indicate the number of strains associated with fatal and severe clinically recognizable infections.

It will be seen that smooth and intermediate smooth variants were usually well capsulated, while nearly two-thirds of the intermediate rough and rough strains showed but little capsular material. All but one of the 28 strains which produced a non-granular type of growth in serum-neopeptone-water were moderately or heavily capsulated, but of the 62 strains which gave a granular growth less than half were well capsulated. The main discrepancy between capsulation and growth characteristics was due to five strains which were heavily capsulated, but which culturally were intermediate rough variants. Four of these differed from all the other *Clostridium welchii* strains studied in regard to size, especially in the primary cultures in meat broth, in which they tended to be double the size of the average *Clostridium welchii*.

As shown in Table I, there were 10 strains which were associated with very severe infections. All of these were heavily capsulated.

Of the strains from 13 cases in which there were no symptoms of severe infection and in which *Clostridium welchii* was cultivated from both the vagina and the

uterine contents, six showed very little capsular material, six were moderately capsulated, and one was heavily capsulated. The last-mentioned strain was one of the five heavily capsulated strains of which individual bacilli were much larger than the normal and which culturally were intermediate rough variants. None of these five strains was associated with severe infection.

Cultures were made from the urine in 26 cases in which the vaginal cultures showed poorly capsulated strains of *Clostridium welchii* and in 56 cases in which the organisms in the vaginal cultures were moderately or heavily capsulated. Only two patients of the first group harboured *Clostridium welchii* in the urine, while of the latter group 33 did so.

These observations suggest that strains which fail to show definite capsule formation in the primary broth cultures do not cause severe infections, and that such strains, if present in the uterine contents, are unlikely to spread beyond the endometrium. At present it is the practice in this laboratory to report such strains as "probably not pathogenic", the term "pathogenic" being used in the sense of being able to give rise to the clinical signs of infection with *Clostridium welchii*. Of the 230 vaginal cultures showing *Clostridium welchii* which were studied for capsule formation, 140, or 61%, showed strains which were regarded as "probably not pathogenic".

A further 64, or 28%, of the vaginal cultures showed strains which were only moderately capsulated. One of these strains was obtained from a patient with bacteriæmia due to *Clostridium welchii*. Clinically, however, this case was not regarded as a severe *Clostridium welchii* infection.

These moderately capsulated strains are reported as "potentially pathogenic", since as a group they appear to be intermediate between the poorly capsulated strains and the heavily capsulated type. The latter strains are regarded as "probably highly pathogenic", since all the strains causing the very severe infections have been of this nature.

Examined in this way, vaginal cultures are of decided value for the rapid bacteriological diagnosis of *Clostridium welchii* infection. The detection of a heavily capsulated strain in the vaginal culture should immediately arouse suspicion of a severe infection. But if the bacilli in the vaginal culture are only slightly capsulated, a serious infection due to *Clostridium welchii* is unlikely.

The Examination of Cervical Smears.

Another line of inquiry which was followed was the examination of cervical smears for heavily capsulated bacilli resembling *Clostridium welchii*.

Two smears were made from the cervical swab. The first was stained with Jensen's modification of Gram's stain. If typical Gram-positive rods were seen, the second smear was stained according to the method of Richard Muir.

Heavily capsulated rods were present in the smears from five patients who died as the result of *Clostridium welchii* infection. In each of these cases similarly capsulated bacilli were seen in the vaginal cultures. In three symptomless cases in which heavily capsulated strains of *Clostridium welchii* were present in the vaginal cultures, organisms resembling *Clostridium welchii* could not be demonstrated in the cervical smears.

Smears were also examined from 21 patients who showed "potentially pathogenic" strains in the vaginal cultures, and who did not present the clinical symptoms of a severe *Clostridium welchii* infection. Heavily capsulated bacilli, thought to resemble those seen in fatal infections, were seen in the smears from two cases; moderately capsulated bacilli were demonstrated in six instances, slightly capsulated bacilli in two, uncapsulated bacilli in two, and in nine no organisms resembling *Clostridium welchii* were seen.

In seven cases in which, on admission to hospital, *Clostridium welchii* infection was suspected on clinical grounds, but in which subsequent investigations disproved this suggestion, no organisms resembling *Clostridium welchii* were seen in the cervical smears.

It appears that in the absence of heavily capsulated *Clostridium welchii* in the cervical smear the possibility of a severe infection due to this organism is unlikely and that the finding of such bacilli in the smear, although not diagnostic of a severe infection, suggests this possibility.

Discussion.

The isolation of *Clostridium welchii* from the vagina, from the uterine contents or from the urine is not in itself a certain indication that the patient is suffering or will suffer from a serious infection due to this organism. Nor will the isolation of this organism from the blood always be of diagnostic value, since *Clostridium welchii* is occasionally cultivated from the blood of women who are not seriously ill.

The work presented in this paper suggests that the solution of the problem of the bacteriological diagnosis of the severe forms of abortifol infections due to *Clostridium welchii* lies in the recognition of the profound variation that occurs with this organism and in the development of methods for the recognition of those variants capable of giving rise to serious infection.

It was found that only a minority of the strains recovered from the vaginal cultures were smooth variants, as judged by surface colony form. In general, colony form was correlated with the type of growth in serum-neopeptone-water, the granularity of the growth in this medium increasing with the increasing roughness of the surface colonies.

There was also fair agreement between the degree of capsulation in the primary cultures in meat broth and growth characteristics, capsulation diminishing with increasing roughness.

Among the strains studied there were 13 which had caused very severe infections. Eleven of these proved to be smooth variants. Not all smooth variants, however, appeared capable of causing severe infection, since 10 such strains were recognized among 97 isolated from patients who were not suffering from a serious infection due to *Clostridium welchii*.

Ten of the strains associated with the severe infections were among those studied for capsulation in the primary broth cultures from the vaginal swab. Every one of these ten strains was heavily capsulated, whereas among 220 strains not associated with severe infections only 16 were heavily capsulated.

The association of severity of infection with both colony form and capsulation is striking, when it is remembered that no attempt was made to determine the toxin production of most of these strains or to assess the possible role of the aerobic organisms which were so often present in the uterus.

At present it is impossible to say whether the observation of growth characteristics or of capsulation is the more reliable as an indication of pathogenicity; but the latter observation can be made much more rapidly than the former.

The examination of cervical smears for heavily capsulated bacilli resembling *Clostridium welchii* has sometimes proved a rapid means of assessing the significance of a heavily capsulated strain in the vaginal culture. Cervical smears may also provide immediate information in cases in which the clinical symptoms suggest the possibility of a severe *Clostridium welchii* infection. In severe cases heavily capsulated forms are to be expected in the cervical smears, whereas in the absence of severe infection due to *Clostridium welchii* such forms are unusual. It is hoped that further experience in the examination of cervical smears will enable the severe cases to be detected with a considerable degree of certainty.

The behaviour of the *Clostridium welchii* strains in serum-neopeptone-water needs further investigation. Some strains, including most of those associated with the severe infections characterized by jaundice and gross blood destruction, grew diffusely. Smears from this type of growth showed capsulated bacilli, usually arranged

singly or in pairs. But the majority of *Clostridium welchii* strains—and these included most of the strains which were not associated with severe infections—grew in serum-neopeptone-water as a rough granular deposit. These granules of growth were usually composed of masses of uncapsulated organisms and chains of sporing bacilli. In 1% neopeptone in water without the addition of serum all the strains grew diffusely, although the growth was often poor.

One possible explanation of the differing types of growth produced in serum-neopeptone-water is that a high concentration of serum is inhibitory to many strains of *Clostridium welchii* and interferes with normal growth. I would suggest that the strains which grow diffusely are those which are able to synthesize some substance, apparently associated with the capsule, which protects them from the inhibitory action of serum.

Summary.

1. In 394 (or 27%) of 1,480 abortional cases *Clostridium welchii* was present in the cultures made from the vaginal swab. Of the women harbouring *Clostridium welchii* in the vagina, 169 were without symptoms of infection, 133 were febrile for three days or less, and 92 showed signs of more serious infection. Of this last group only 15 suffered from a severe clinically recognizable infection due to *Clostridium welchii*.

2. Of 241 consecutive cases of incomplete abortion *Clostridium welchii* was obtained from both the vagina and uterine contents in 37, from the vagina only in 29, and from the uterine contents only in four. In 17 of the 41 cases in which *Clostridium welchii* was detected in the uterine contents there were no symptoms of infection.

3. *Clostridium welchii* was cultivated from the urine in 12 out of 14 severe cases of infection due to this organism, in 18 out of 35 septic cases in which the clinical signs were not thought to be due to a severe *Clostridium welchii* infection, and in eight out of 38 cases in which symptoms of infection were mild or absent.

4. Of 110 strains examined for colony form, only 20 were typical smooth variants. The remaining 90 strains showed surface colonies of varying degrees of roughness. Cultural differences were also apparent when the strains were grown in a mixture of 1% neopeptone in water and normal horse serum. Smooth strains tended to give a diffuse growth, while strains which gave rough or partially rough surface colonies produced a flocculent granular growth. All but two of the strains causing severe infections produced smooth surface colonies, and all but three gave a non-granular growth in serum-neopeptone-water.

5. Of 230 consecutive strains of *Clostridium welchii* for which the degree of capsulation in the primary cultures in meat broth was recorded, 26 were heavily capsulated, 64 were moderately capsulated and 140 showed very little capsular material. Ten strains which gave rise to severe infections were all heavily capsulated. Not one of the poorly capsulated strains caused serious infection.

6. An examination of cervical smears from 36 patients showed that in severe infections heavily capsulated bacilli could be demonstrated in the smears, whereas in the absence of severe infection due to *Clostridium welchii* heavily capsulated rods were unusual.

7. The investigations here recorded indicate that the bacteriological diagnosis of the severe forms of abortional infections due to *Clostridium welchii* depends on the recognition of those variants capable of initiating severe infection.

Acknowledgement.

I wish to express my thanks to Dr. Arthur M. Hill for his help in classifying the cases.

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THE CASE OF THE PRINCESS CHARLOTTE.

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THE wind and the rain of a midwinter's night early in 1818 prevented a lying-in household of Miss Cotton, Wimpole Street, Cavendish Square, from hearing two shots that were fired in an upstairs bedroom; but their result was seen by a frightened manservant next morning when he discovered the shattered head of his master, Sir Richard Croft, the well-known accoucheur. The coroner's verdict was insanity, for Sir Richard had been observed, during the difficult labour he had most hesitatingly conducted the previous night, to be profoundly depressed, as well Sir Richard might be, for the past three months had been for him a veritable nightmare of anxiety and worry. Not for one minute had he been able to subdue the turbulent memory of three dreadful nights in the previous November, as a result of which fashionable and professional London had so branded him that his reputation and practice had, in so short a time, dwindled almost to vanishing point; driven to distraction, he could face the world no longer.

It was the writing of Lytton Strachey, that most peerless of latter-day biographers, which first introduced me to Sir Richard Croft; and so, when I was in America in 1937, I took advantage of the splendid service at the Army Medical Library (formerly the Surgeon-General's Library) in Washington to collect the details of the part played by this luckless accoucheur in the tragic case of the Princess Charlotte; and these I briefly present to you tonight.

I am sure that many of this audience have driven not once, but many times, out of London on a long summer's afternoon to Windsor and Eton. When on this route, if one turns to the left instead of crossing to the north side

¹ Read at a meeting of the Section of Obstetrics and Gynecology of the Victorian Branch of the British Medical Association on July 16, 1940.

of the Thames at Surbiton, the road leads on to Esher. At Esher those interested in the sport of kings may inspect the Sandown Park racecourse, while others, more interested in the domestic expressions of power and kingship, will drive up to the gates of the nearby Claremont Park, for this has been the home of more than one highly placed and ill-starred figure whose life and death have profoundly influenced the history of England and of Europe. The stately old mansion of Claremont was built in 1768 by the brothers Adam for the founder of British India, Robert Clive, whose forty-nine years of heroic action ended so tragically in 1774. Thirty-two years later it was selected as the household of Prince Leopold (of the small and, up to that time, unimportant German duchy of Saxe-Coburg) and his young bride, the Princess Charlotte, presumptive heir to the English throne. On her death twelve months later Leopold left for Brussels, there to found the dynasty of the present Belgian royal house (the reigning King of the Belgians is his grandson). In this same house, too, died in 1854 Louis Philippe, King of France, who had fled from the revolutionary Parisian mobs of 1838. In 1882 it became the property of Queen Victoria, and then settled on the old house a long period of staid and uneventful happenings which have continued to the present day; but in the first week of November, 1817, many minds in England were eagerly directed to Claremont Park, for the Princess Charlotte was almost any day expecting to be confined.

The British nation of that time had little reason to admire its rulers. George III was blind and practically insane, and the gay Prince Regent had little or nothing to commend him. In addition, times were particularly bad; the Napoleonic war had ended after a long exhausting struggle only two years before, and all branches of trade and commerce were profoundly depressed; unemployment was widespread, and riots and noisy gatherings were developing throughout the country.

For some time past all hopes had been centred in the young and recently married Princess Charlotte, and her popularity developed the more strongly when it was known that she was expecting a child who might one day rule from the English throne in succession to its mother. The extraordinary interest in the forthcoming event was evidenced by the heavy wagers being laid on the sex of the expected infant; the financial captains of the stock exchange calculated that a princess would raise the price of consols $2\frac{1}{2}\%$, while a prince would be good for at least 6% ; but none of these speculators could hear the beating of the wings of the Angel of Death that was hovering over Claremont. The Princess, supposedly quite healthy and certainly young, for she had just celebrated her twenty-first birthday, went into labour on Monday, November 1, attended by the most prominent accoucheurs of the day. By Thursday morning an anxious public had learnt that both she and her baby boy were dead. "The royal kaleidoscope had suddenly shifted and nobody could tell how the new pattern would arrange itself."

Who were the *dramatis personae* in the obstetrical tragedy which immediately initiated throughout the kingdom a multitude of angry and resentful inquiries for a searching investigation into the cause of its happening?

First of all there was the Princess Charlotte herself. The Princess Charlotte was the only child of the Prince Regent (afterwards George IV), who was the eldest son of George III, and her mother was Caroline of Brunswick. At the time of which I speak she was twenty-one years of age; her life before marriage had not been a happy one. Since her birth her parents had unceasingly quarrelled over who should exercise control, with the result that she had grown into a wild impetuous young woman, possessed of few good manners and little of that self-control desired of a princess. Of fair complexion, she was rather below middle height, and although slightly pitted by smallpox, was not without personal attractions. After two or three brisk flirtations, at last she found the proper man to develop her good qualities in the person of Prince Leopold of Saxe-Coburg, five years her senior when they were married in 1816. The character of Leopold—destined later to be a notable Belgian king—contrasted strongly

with that of his wife. He was cold in manner, formal in speech and careful in action, and he quickly dominated, and, somewhat strangely it would appear, inspired a deep affection in the tempestuous creature by his side. At the time of her confinement they had enjoyed eighteen months of unclouded married life.

There were three doctors directly associated with the confinement. The first was the Princess's physician-in-ordinary, Dr. Matthew Baillie, aged fifty-six years, an eminent physician of Saint George's Hospital. Baillie, a Scotchman, whose mother was a sister of the famous John and William Hunter, was married to a daughter of Dr. Thomas Denman, who had been the leading accoucheur in London until his death a year or two before. Another daughter was married to a Sir Richard Croft, and it was he who had been selected to conduct the very important confinement. Croft was fifty-five years of age and he was a baronet, not on account of any deservedly high standing in the medical profession, but because on the death of his brother a year before the family baronetcy had fallen to him. His association with the Princess was probably due to his brother-in-law's sponsoring, and also because, having succeeded to his father-in-law's fashionable obstetrical connexion, he had recently successfully delivered the influential Duchess of Devonshire. Being interested in Croft's qualifications, I wrote some time ago to Dr. Stallworthy, one time New Zealand obstetric scholar at the Women's Hospital and now first assistant in the Nuffield Department of Obstetrics and Gynaecology at Oxford, and he has learnt from the Oxford historian, Mr. B. M. Pycroft, that Croft was not a Licentiate of the Royal College of Physicians, nor was he a member of the Surgeon's Company or of the Royal College of Surgeons; the Surgeon's Company had become the Royal College of Surgeons of England when a royal charter had been granted in 1800. So apparently Croft possessed no genuine medical or surgical qualifications, though he had been at one time a student at "Barts." As late as this period archbishops and others of the ecclesiastical hierarchy had power to grant licences-to-practice, known as episcopal licences; but Croft's name was not on this register. He termed himself a *chirurgus privilegiatus* of Oxford; but this title had no connexion with the University of Oxford, though such the term would imply. It was known, however, that Croft had practised for some time in that city, and it seems most probable that he held a licence, not from any statutory authority, but from either a member of the Royal family or a member of the aristocracy powerful enough to protect him from being regarded, by the medical profession at least, as a charlatan. It will be remembered that not until the *Medical Act* of 1858 was any legal distinction drawn between properly qualified and non-qualified practitioners; even now, in this year of grace 1940, there is no legal barrier either in Great Britain or in Australia to the non-qualified practising medicine or surgery or its specialties. As might be expected, Croft held no hospital appointments; he was, however, attached to the Charity for delivering poor married women in their homes, and this organization exists today under the title of the Royal Maternity Charity. Associated with Croft in this Charity was Dr. John Sims, aged sixty-nine years, who possessed a reputation in the use of instruments in obstetrics, and it was he whom Croft called in when Princess Charlotte's delivery was unduly delayed. (This Sims was not the designer of the Sims speculum, nor did he describe the Sims position; these were due to an American, Dr. Marion Sims, born in 1813.)

But in addition to Croft, Baillie and Sims, there was another doctor in the house at Claremont. He was a resident member of the household and the personal physician of Prince Leopold. His quiet room was situated in a distant wing of the mansion, well removed from the lying-in chamber. His name was Dr. Christian Stockmar, and at this time there was no indication of what fate had in store for this young German. Dyspeptic in constitution, melancholic by temperament, he was probably not then known to the Archbishop of Canterbury and the Ministers of State, who had assembled to be present at the birth of the heir to the throne. But Stockmar was to be much

more in their thoughts two or three decades later, when he probably was the most influential man in Europe. At the time of which I speak few people outside Germany knew anything more about Coburg than that it was the capital town of the small duchy of Saxe-Coburg, one of the numerous petty German States, and today incorporated in the modern Bavaria. Here circumstances were such that a young man of ambition, whether of princely or of humble origin, had to seek opportunity elsewhere. But barely a generation later much more information was available about Coburg; a Coburger sat on Belgium's new throne, after being invited to become King of Greece; another occupied the Portuguese throne; in Brazil, the wife of the Emperor came from Coburg, and even the husband of Victoria of England came from that small German town. A few years later still the Empress of Germany was a Coburger, and a branch of the family reigned in Bulgaria; this amazing rise of the House of Coburg was due to the wisdom and devotion of one man, Dr. Christian Friedrich Stockmar. Many years later Stockmar wrote:

It was a clever stroke to have originally studied medicine: without the knowledge thus acquired, without the psychological and physiological experiences which I thus obtained, my *savoir-faire* would have often gone abegging.

At Claremont, Stockmar was not completely at home, for this England was very different from his beloved Coburg, and the other members of the court were rather disdainful of the little plebeian foreign doctor; he occupied his spare time in studying English history and English constitutional questions and in recording acutely accurate character studies of all the persons he saw at the court. In his memoirs we learn that sometimes the Iron Duke had his mind not on the playing fields of Eton, but on certain indoor sports, for at table Wellington was fond of whispering rather improper stories to the Princess. Stockmar had no aristocratic antecedent. He was the son of a minor magistrate in Coburg, and after taking part as regimental medical officer in the Napoleonic wars, had settled down to practise in his native town, where he had met Prince Leopold, and had impressed the latter so much with his ability that appointment as the Prince's personal physician followed and together they came to England. With the Princess Stockmar was soon on the best of terms, for in spite of poor health he was fond of a little homely fun, and at times could be very witty, though in a strictly virtuous way. He had watched the happiness of the husband and wife at Claremont with the greatest approbation, but this had not tempted him to enlarge his medical attentions by becoming physician to the Princess. In this restraint he evidenced a quality of prudent understanding about which all Europe was to learn in the coming years. When in the spring of 1817 it became known that the Princess was expecting a child, the post of one of her physicians-in-ordinary was offered to Stockmar; but he had the good sense to refuse. He quickly perceived that his foreign colleagues would be jealous, and if anything untoward happened, most assuredly the foreign doctor would be blamed. Thus he had nothing to do with Charlotte's confinement and had most firmly refused to have any hand in the management of her pregnancy. In after years he wrote of these months:

I can only thank God that I never allowed myself to be blinded by vanity, but always kept in view the danger that must necessarily accrue to me if I arrogantly and imprudently pushed myself into a place in which a foreigner could never expect to reap honour, but possibly plenty of blame. I knew the hidden rocks too well and knew that the national pride and contempt for foreigners would accord no share of honour to me if the result was favourable and, in an unfavourable issue, would heap all the blame on me. As I had before, at various times, when her physician was not at hand, prescribed for the Princess, these considerations induced me to explain to the Prince that, from the commencement of her pregnancy, I must decline all and any share in the treatment.

Later he continued: "When I recall all the circumstances I feel but too vividly the greatness of the danger which I escaped." Those who remember what happened to Sir Morell Mackenzie seventy years later, when he was called

from London to Berlin to attend the Crown Prince Frederick, who was suffering from a laryngeal cancer, may wish that the resolute Mackenzie had exhibited a like sagacity. But that is another story.

But before I proceed to discuss the Princess's confinement it is of interest to consider the status of English midwifery at that period. British obstetrical science was already a great tradition, coming down from the Chamberlens, Douglas, Smellie, Harvie and William Hunter, and training in this department by lectures and clinical work had been given by Denman and others, although it had not yet taken its place alongside other departments of medicine in university and collegiate courses. It may be noted that the northern capital of Edinburgh, always to the front in the advancement of medicine (with which sentiment I know Professor Marshall Allan finds himself in hearty agreement), had appointed its first professor of midwifery, Dr. Joseph Gibson, in February, 1726. He was actually the first in the world to bear this title, Strasburg not having a university teacher until two years later. Gibson seemed, however, to have confined his lectures to midwives. In spite of the well-established English tradition, the great percentage of practical midwifery was in the hands of midwives, and Princess Charlotte was the first royal person to be attended by a male practitioner. Her grandmother, Queen Charlotte, had been attended in her thirteen confinements by a midwife, Mrs. Draper, with the happiest results. When, however, it was known that the Princess was pregnant and an heir to the throne was so anxiously desired, it was decided to take every possible precaution. (It may be mentioned in passing that doctors who specialized in midwifery were first termed "man midwives" and later "accoucheurs".)

A few words may describe the contributions of the great English obstetricians at this time. As the inventors of the obstetrical forceps—which have been termed the most beneficent of all surgical instruments—the name of the Chamberlens is immortal, though their lustre is somewhat tarnished by the secrecy with which they preserved the invention. This family practised midwifery in England for almost 150 years from the middle of the sixteenth century, and managed to keep the family instruments undisclosed for about 100 years. Partly as a result of this reticence and partly in consequence of their self-sufficient and combative characters, the Chamberlens never enjoyed the confidence of their professional colleagues. It was the possession of the forceps and the knowledge that by their means they could deliver women without injury to mother or child that, added to the Chamberlens' strong personalities, explained their success in practice; and it was the ignorance of the forceps on the part of other male practitioners who, until the forceps became generally known (about 1733), used only destructive instruments and had little experience of normal labour, that partly explained the opposition of the midwives to men practitioners of obstetrics. Meanwhile the Chamberlens went on prospering and profiting by their invention, which was of too high a value and produced results too salutary to be affected by the wild tirades of the midwives and their supporters. The Chamberlens guarded their secret of the iron tongs most closely for about 100 years, but then it began to filter out; it was not, however, until 1733 that they were first made publicly known by Dr. Edward Chapman, nor till June, 1813, that the forceps belonging to the family were found in the walls of a closet in their country house, Woodham Mortimer Hall, near Maldon in Essex. The Chamberlens' forceps, which were straight, are now preserved in the Library of the Royal Society of Medicine, and it is of some interest to note that a Chamberlen obtained patents for the forceps from the Swedish Government in 1669 and from the Danish Government in 1671.

But the greatest of British obstetricians, William Smellie, was a Scotchman who took the degree of doctor of medicine at Glasgow in 1745. Feeling that his outlook in Lanarkshire was not sufficiently promising, like so many of his countrymen he viewed what Johnson called the finest prospect in Scotland—the road to England—and by it came to London in 1738. In spite of his uncultivated

bearing and the bitter opposition of Mrs. Nehill, the Haymarket midwife, who called him "a great horse god-mother of a he-midwife". Smellie acquired a large practice, and William Hunter, brother of the immortal John, came to him as a resident pupil in 1741. It was Smellie who introduced the steel-lock forceps in 1744 and the curved and double-curved forceps during the period 1751 to 1753. His volume on midwifery, published in 1752, was the first book to lay down safe rules for the use of the forceps and for the differentiation of contracted from normal pelves by actual measurement. He discovered, too, how to rotate the head with forceps when it was in the occipito-posterior position. Much was made by Smellie's critics of the frequency with which he was said to use the forceps; but in fact he used them seldom, for he stated that in only 10 out of every 1,000 labours was instrumental delivery required. Smellie was a careful student of Nature's methods; he said of himself: "I diligently attended to the course and operations of Nature which occurred in my practice, regulating and improving myself by that infallible standard." He practised Cæsarean section on several occasions, and mentions the case of the patient operated on in Ireland by Mary Donaley, an illiterate but very skilled midwife, who had the good fortune to save both mother and child. This, in January, 1738, was the first successful case of Cæsarean section in the British Isles.

Records show that Smellie was a kindly cautious man of an artistic temperament, slow of speech and avoiding disputes, not greedy of gain, his principal ambition being to acquire the name of a learned author by those works in which he took such pride. His critics—like all successful men, he had many—complained that in some cases his caution in speech was carried to excess, as, for instance, when "in order to avoid reflections" he kept secret the knowledge that a patient's uterus was ruptured. But the records also indicate that his canny Scotch character obtained him great credit on one occasion, when, operating under the bedclothes, as was the practice of the time, he accidentally divided the cord on the proximal side of the ligature, with the result that a sharp hæmorrhage occurred. Smellie was equal to the occasion; seizing and tying the cord, he told the midwife that this was his way of preventing convulsions in the child. We know, of course, that for many years lesser breeds have whispered that Scotchmen are as cunning as a bagful of monkeys.

Smellie was a great man, regarded by many authorities as one of the most important obstetricians of all times and countries. This view is shared by my colleague Dr. J. S. Green, to whose delightful series of articles "New Lamps for Old", which appeared in *The General Practitioner* two or three years ago, I have had recourse. Smellie lacked the social graces of his pupil, William Hunter, another Scotchman, who eventually became the leading obstetrician and consultant in London. Few men have laboured with such austere devotion to science as did William Hunter. Like Smellie, he was a great believer in Nature's methods; he even opposed the use of forceps, and sometimes exhibited his own instrument, covered with rust, as evidence of the fact that he never used it. "It was a great pity", he wrote, "that the forceps were ever invented; where they save one, they murder twenty."

In relation to his colleagues, Hunter was a jealous, sensitive, highly strung man, who embittered his own life by needless controversies with contemporaries whom he easily overshadowed. We may contrast his noble gift of a museum worth £100,000 to the city of Glasgow with the self-denying stoicism of his private life. He worked till he dropped and lectured whilst he was dying. William Hunter claimed the discovery of the placental circulation, which was contested by his younger brother John. The dispute led to their separation and the quarrel was never settled. Although John attended William in his last illness, he was not present at his funeral and received no bequest in his will.

William Hunter's nephew was Matthew Baillie, Princess Charlotte's physician.

After the death of William Hunter, in 1783, the leading obstetrical practice in London passed to Thomas Denman, who, as ship's surgeon, had saved enough prize money

during actions against the French Fleet in the West Indies to take the degree of Doctor of Medicine at Aberdeen in 1764. He eventually developed a very extensive practice in addition to becoming a distinguished teacher and writer on midwifery. His reputation rests firmly on two of his works, his "Aphorisms" and his "Introduction to the Practice of Midwifery", published at the age of sixty-one years, when he was an accoucheur of ripe experience and had been a teacher of midwifery for many years. Dr. Herbert Spencer, writing in 1927, claimed that Denman's "Introduction to the Practice of Midwifery" was perhaps the most splendid work on midwifery in the English language, whether regarded from the point of view of format, paper, printing and illustrations of the work, the learning and knowledge it exhibits, or from the ordered, lucid and judicial manner in which that knowledge is presented. This book is also noteworthy because it contains an account of the origin and mode of employment of that purely English operation, induction of premature labour in cases of contracted pelvis. It was chiefly due to Denman's adoption and judicious advocacy that the operation became a favourite one in England long before it was accepted abroad. Besides a son named Thomas, who became Lord Chief Justice of England, Denman had twin daughters, one of whom married Richard Croft, to whom, in Denman's later years, passed most of his fashionable practice, and the other married Dr. Matthew Baillie. Denman died in 1815, at the age of eighty-two years. In the conduct of labour, Denman, like Smellie and Hunter, was a great admirer and imitator of Nature, and his use of instruments was very limited.

It will thus be seen that the characteristic of British midwifery at the beginning of the nineteenth century was one of strong conservatism, with a firm belief in the resources of that "perfect operatrix"—Nature—in effecting delivery. In the light of present knowledge it would be interesting to know the occurrence of puerperal fever in the practice of the leading obstetricians, who before the employment of antiseptics were daily engaged in dissections. It is stated that in three months at the Brownlow Street Hospital, 23 women suffered from sepsis and only one recovered; perhaps it was such occurrences which induced Smellie, Hunter and Denman to leave their patients in labour to Nature and the midwife.

Throughout the eighteenth century obstetricians paid particular attention to the diet, hygiene and evacuations of the patient. Bleeding was regarded as of great value in many disorders, and was also used as a prophylactic against toxæmia. In the case of small women of the size of Princess Charlotte, many recommended reduction of the size of the child by purgatives and restricted diet (a practice first carried out by Lucas, of Leeds, in 1794).

Richard Croft and Matthew Baillie both received their obstetrical training from their father-in-law, Thomas Denman, and it is apparent that in the management of the pregnancy and confinement of the Princess, Croft and Baillie were under the influence of the conservative teaching of Denman and his great predecessors, Smellie and Hunter.

In the later months of her pregnancy the Princess Charlotte had been subjected to the then fashionable "lowering" treatment of restricted dieting, aperients and frequent bleedings, and could not have been in the best of condition to stand the prolonged confinement which began at seven o'clock on Monday evening, November 5. The only account—and this is far from complete—of the labour which I could unearth was given by Dr. John Sims to his friend Dr. Joseph Clarke, of Dublin, in a letter written a few days after the catastrophe, and it is quoted by Dr. W. S. Playfair in *The Medical Times and Gazette* of December 7, 1872. With Sir Richard Croft and his assistant, Dr. Matthew Baillie, in attendance, the labour commenced by rupture of the membranes at seven o'clock on the Monday evening and the contractions followed soon after. They continued through the night and a greater part of the next day, and were sharp, soft and very ineffectual. Towards Tuesday evening Croft began to suspect that the labour might not be terminated without artificial assistance, and a message was dispatched for

Dr. John Sims, who arrived at 2 a.m. on Wednesday. The labour was now progressing more favourably, and both Baillie and Sims concurred that the use of instruments should not be entertained. (In passing, it might be remembered that this was thirty years before the introduction of anaesthetics). From this hour until the termination of labour the progress was uniform, though very slow. The royal patient was in good spirits, with a calm pulse; but at six o'clock that evening the passage of meconium led to the suspicion that the child might be dead. The consultants still considered that instrumentation was out of the question, for the contractions were now more effectual and the labour was proceeding regularly but slowly. The child (a boy) was born lifeless at nine o'clock in the evening, and all attempts to reanimate it were without effect. Soon after delivery, so the description runs, Sir Richard discovered that the uterus was contracted in the middle in the hour-glass form, and as some hæmorrhage occurred it was agreed that the placenta should be removed manually. This was done about half an hour after delivery, with more ease and less hæmorrhage than usual. Her Royal Highness continued well for about two hours; she then complained of feeling nauseated, tinnitus appeared, and her pulse rate became rapid; later she became quiet and her pulse less frequent; but at half past twelve she complained of severe pain in the chest and became extremely restless, with a rapid, weak and irregular pulse. It was obvious that she was dying, and Stockmar in his memoirs graphically describes the last moments:

Baillie sent word that he wished me to see the Princess. I hesitated but at last went with him. She was suffering from spasm in the chest and difficulty in breathing, in great pain and very restless; she threw herself continually from one side of the bed to the other, speaking now to Baillie, now to Croft. Baillie said to her "Here comes an old friend of yours". She held out her hand to me hastily and pressed mine warmly twice. "They have made me tipsy with wine", she said. After a little I left her and was already in the next room when I heard her call out in her loud voice "Stocky, Stocky". As I ran back the death rattle was in her throat. She tossed herself violently from side to side; then suddenly drew up her legs, and it was over.

Dr. Sims gives the briefest of accounts of the autopsy which was subsequently performed. He describes that two ounces of blood-stained fluid, supposed to be thrown out *in articulo mortis*, were found in the pericardium. The brain and other organs were all sound, except the right ovary, which was distended into a cyst the size of a hen's egg. The hour-glass contraction of the uterus (which extended upwards as high as the navel) was still visible, and there was considerable blood in its cavity but those present were in dispute about the quantity, the estimates varying from 12 to 30 ounces.

Playfair's commentary on the case seems sound enough today, even though it was written sixty-eight years ago. This is what he wrote then in *The Medical Times and Gazette*:

What are the facts here shown? Here was a delicate young woman prepared for the trial before her by the lowering of her organic strength by bleeding, aperients and low diet, and who was allowed to go on in feeble labour for no less than fifty-two hours after the escape of the *liquor amnii*. Such was the groundless dread of instrumental interference then prevalent, that although the case dragged on its weary length with feeble ineffectual pains it was stated "there never was room to entertain a question about the use of instruments". Can any reasonable man doubt that if the forceps had been employed hours and hours before—say on Tuesday, when the pains fell off—the result would probably have been very different and that the life of the child, destroyed by the enormously prolonged second stage, would have been saved. It would be difficult to find a case which more forcibly illustrates the danger of delay in the second stage of labour. Then what follows? The uterus, exhausted by the lengthy efforts it should have been spared, fails to contract effectually; nor do we hear of any attempts to produce contraction by pressure. The relaxed organ becomes full of clots, extending up to the umbilicus, and all the characteristic symptoms of concealed post-partum hæmorrhage develop. Before long other symptoms came on, graphically described by Baron Stockmar, and which point to the formation of a clot in the heart and pulmonary

arteries—a most likely occurrence after such a history. Here was evidently something different from the exhaustion of hæmorrhage and no one who has witnessed a case of pulmonary obstruction can fail to recognize in this account an accurate delineation of its dreadful symptoms. Surely this lamentable story can only lead to the conclusion that the unhappy and gifted Princess fell a victim to the dread of that bugbear "meddlesome midwifery" which has so long retarded the progress of medicine.

In the issue of *Surgery, Gynecology and Obstetrics* of July, 1938, Professor E. C. Irving, of Boston, quoted Kellogg as writing that the cause of the Princess's death was ante-partum hæmorrhage; but it will be readily agreed that there is little in the available evidence to support Kellogg's statement.

A veritable flood of contumely in the form of abusive pamphlets and social and professional ostracism, from which his title of baronetcy offered no protection (though the royal family was said to be most considerate and sympathetic) soon descended on the head of the ill-fated and inept royal accoucheur, and the tragic sequel to the catastrophe was not long delayed. The Croft baronetcy did not become extinct with Sir Richard's death; the father of the present eleventh baronet was killed by a Turkish bullet in the fateful month of August, 1915, on the shore of the blue Ægean Sea. Sir Richard's brother-in-law, Thomas Denman, who became Lord Chief Justice of England, was created Baron Denman, and his descendant, Lord Denman, was Governor-General of our Commonwealth during the years from 1911 to 1914.

Dr. Matthew Baillie died of tuberculosis in 1823, and is commemorated by a bust and inscription in Westminster Abbey. A famous old gold-headed cane, which had descended from Radcliffe, Mead, Askew and Pitcairn to Baillie, was presented by his widow to the Royal College of Physicians, and is preserved there, with the arms of the successive possessors engraved thereon. This gold-headed cane was the subject of a volume describing its five owners and their works, and it is often quoted in the medical history of the eighteenth century.

Charlotte's father was crowned George IV two years after her death; but he had cirrhotic liver (and a belly so pendulous that even corsets could not support it), which claimed him as a victim ten years later, when his brother ascended the throne as William IV. The next in succession was their young niece, Victoria, whose sixty-four years of queenship commenced on June 20, 1837; and so, all because an unskilful and overwrought accoucheur neglected to grasp a post-partum fundus, the Victorian era was born.

GAS TENSIONS IN THE TISSUES IN PHYSIOLOGICAL CONDITIONS.

By ERIC W. SIRREE.

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Changes in Respiration.

Forced Breathing.

CAMPBELL⁽¹⁾⁽²⁾⁽³⁾ found that artificial respiration on animals greatly reduced both the carbon dioxide tension (by as much as 44 millimetres of mercury) and the oxygen tension in the tissues. No details of the experiments are given. In the present investigation, by methods previously discussed⁽¹⁾⁽²⁾⁽³⁾ it was found that manual artificial respiration on rabbits regularly produced a slight fall of carbon dioxide tension both under the skin and in the peritoneal cavity. Changes in oxygen tension were slight and inconsistent, but showed a general tendency to a rise in both tissue sites.

In the human subject it was found that forced breathing caused a pronounced fall in alveolar and subcutaneous

¹ Work done with the aid of a grant from the National Health and Medical Research Council.

carbon dioxide tensions with corresponding rises in oxygen tension (Table I). The rise in subcutaneous oxygen tension was not usually more than two or three millimetres of mercury.

Apnoea.

Cessation or diminution of breathing was produced in rabbits for periods of from two to seven minutes by gentle compression of the thorax, which produced remarkably little struggling. One animal became unconscious in five minutes. The carbon dioxide tension under the skin and in the peritoneal cavity was much raised at the end of the experiment. In the recovery period (five to fifteen minutes) the carbon dioxide tension decreased down to or below the normal level. Changes in oxygen tension were slight and irregular, with a general tendency in the opposite direction to carbon dioxide tension changes. Similar changes in subcutaneous gas tensions in the human subject were noted with voluntary apnoea as shown in Table I, in which the effects of successive changes in respiration are also given.

TABLE I.

Gas Tensions in the Subcutaneous Tissues and the Expiratory Alveolar Air.

Condition of Respiration.	Subcutaneous Tissues.		Alveolar Air (Expiratory).	
	Carbon Dioxide. (Millimetres of Mercury.)	Oxygen. (Millimetres of Mercury.)	Carbon Dioxide. (Millimetres of Mercury.)	Oxygen. (Millimetres of Mercury.)
Normal	47	21	42	91
Forced breathing (approximately 45 litres per minute)				
6 minutes	30	23	27	122
25 minutes	21	26	16	134
Recovery—				
10 minutes	49	16	45	67
60 minutes	46	23	42	90
Normal	45	18	41	91
Apnoea—90 seconds	54	16	59	43
Recovery—5 minutes	43	19	42	94
Normal	47	18	42	92
Apnoea—110 seconds	73	13	62	40
Forced breathing—3 minutes	33	21	25	131
Recovery—4 minutes	43	19	40	97

Changes in the Composition of Inspired Air.

Increase of Inspired Oxygen Percentage.

Campbell⁽¹⁰⁾ made observations on rabbits breathing air with high oxygen percentage (56% or more) for long periods, in which gas tensions in the tissues became stabilized. He found that the peritoneal oxygen tension rose only five or ten millimetres of mercury. The subcutaneous oxygen tension rose only two or three millimetres of mercury and tended to return to normal during the experiment. There was a corresponding rise of carbon dioxide tension in both sites of about five millimetres of mercury.

Results similar to those given by Campbell were obtained in the present investigations for changes of subcutaneous gas tensions in rabbits breathing 40% to 50% oxygen for an hour. A rise in both carbon dioxide tension and oxygen tension in the subcutaneous tissues of a human subject breathing 50% oxygen was also found (Table II).

Decrease of Inspired Oxygen Percentage.

Campbell⁽¹⁰⁾ found that the inspiration of low oxygen percentages (about 11%) by rabbits for prolonged periods caused the opposite effects to the breathing of high oxygen percentages. Both the subcutaneous and the peritoneal carbon dioxide and oxygen tensions were lowered by about eight or ten millimetres of mercury. These results have been confirmed (in subcutaneous tissues only) in rabbits breathing low oxygen percentages for two hours, and similar results were obtained from one experiment on a normal human subject (Table II) breathing 10% oxygen.

The subject was extremely dyspnoeic at the end of the experiment, which lasted twenty-two minutes, and he was showing definite mental effects of anoxaemia.

TABLE II.

Gas Tensions in the Subcutaneous Tissues and in the Expiratory Alveolar Air

Approximate Percentage of Carbon Dioxide and Oxygen in Inspired Air.			Subcutaneous Tissues.		Alveolar Air (Expiratory).	
Carbon Dioxide.	Oxygen.	Duration of Breathing.	Carbon Dioxide. (Millimetres of Mercury.)	Oxygen. (Millimetres of Mercury.)	Carbon Dioxide. (Millimetres of Mercury.)	Oxygen. (Millimetres of Mercury.)
	21		48	18	41	97
	50	12 minutes.	52	18		
	50	33 minutes.	54	21	40	297
	21		45	20	40	98
	10	15 minutes.	39	15		
	10	22 minutes.	37	12 ¹	35	38
5.4	21		52	9	40	96
	20	10 minutes.	56	10		
5.4	20	15 minutes.	59	14	47	123
	21	5 minutes.	48	12	40	100
	21		48	17	41	92
4.6	49	10 minutes.	59	23		
4.6	49	15 minutes.	60	30	46	306

¹ Sample contaminated by blood. True oxygen tension probably appreciably lower than 12 millimetres of mercury.

Increase of Inspired Carbon Dioxide Percentage.

Campbell⁽¹⁰⁾ found that in animals breathing a high percentage of carbon dioxide (for example, 30%) there was a pronounced increase in the carbon dioxide tension in the tissues without appreciable effect on the oxygen tension.

In the present series, observations were made on the subcutaneous tissues in two rabbits breathing about 7% carbon dioxide for one and a half to two hours. Great increases in the subcutaneous oxygen tension (seven millimetres of mercury and twelve millimetres of mercury) were noted, as well as increases in subcutaneous carbon dioxide tension (25 millimetres of mercury and 19 millimetres of mercury). The subcutaneous oxygen tension remained high for several hours after the experiments. Experiments on human subcutaneous tissues gave similar results (Table II).

Increase of Inspired Carbon Dioxide and Oxygen Percentages.

As would be expected, the inspiration of air containing an increase in the percentages of both carbon dioxide and oxygen was found to cause a pronounced rise in the subcutaneous tensions of both gases. Thus, in one experiment, the inspiration for two hours of a gas mixture containing 8% carbon dioxide and 40% oxygen by a rabbit gave a rise of subcutaneous carbon dioxide tension from 49 to 93 millimetres of mercury and a rise of subcutaneous oxygen tension from 19 to 29 millimetres of mercury. Corresponding results were noted in a similar experiment on a human subject (Table II).

Increase of Inspired Carbon Dioxide Percentage and Decrease of Inspired Oxygen Percentage.

In two experiments on rabbits, mixtures of about 7% carbon dioxide and 10% oxygen were inspired for periods of one and a half and three hours. Increases of subcutaneous carbon dioxide tension (22 millimetres of mercury and 28 millimetres of mercury) and decreases of subcutaneous oxygen tension (6 millimetres of mercury and 16 millimetres of mercury) were noted.

The Effects of Changes in Respiration and Inspired Air.

The results of the experiment on forced breathing (Table I) show clearly a pendulum-swing effect, noted also in other types of experiments, in which the gas

tensions in the tissues and alveolar air not only returned to normal after the appropriate stimulus had ceased, but overshoot the mark.

The effects of voluntary apnoea (Table I) show that changes in gas tensions in the tissues can occur very rapidly, although they are not always as noticeable as in the experiment quoted. Changes occurring in the loculated gas depots in human subcutaneous tissues are naturally more rapid than in the large baggy gas depots in rabbits. An intraperitoneal injection of 400 cubic centimetres of carbon dioxide in a rabbit was nearly all absorbed in one hour. A rise of subcutaneous oxygen tension of two millimetres of mercury noted one hour after the intraperitoneal injection of carbon dioxide may have been caused by hyperpnoea, which the animal exhibited.

In contradistinction to Campbell's findings, it is shown that forced breathing caused a rise in subcutaneous oxygen tension, as would be expected from the rise in alveolar oxygen tension, together with a pronounced fall in carbon dioxide tension in alveolar air and tissues. Apnoea had the opposite effect. The breathing of air with a high or low oxygen content caused changes in oxygen tension in the tissues in the same direction as the changes occurring with forced breathing and apnoea respectively. In each case the direction of change of oxygen tension in the tissues followed the change of alveolar oxygen tension.

Both forced breathing and the inspiration of low oxygen percentages caused a fall of carbon dioxide tension in alveolar air and secondarily in the tissues, as would be expected from the hyperventilation in these conditions. Apnoea caused a rise of carbon dioxide tension in alveolar air and tissues for obvious reasons. The rise of carbon dioxide tension and fall of oxygen tension caused by apnoea is similar to the effects of breathing a high percentage of carbon dioxide and a low percentage of oxygen. The rise of carbon dioxide tension in the tissues when high percentages of oxygen are breathed is due possibly to a decrease in the circulation rate, either general or local, or both.

The breathing of high percentages of carbon dioxide caused hyperpnoea, so that the tensions of both carbon dioxide and oxygen were increased in alveolar air and tissues. It should be noted that the inspiration of increased percentages of either carbon dioxide or oxygen caused a rise of tension of both gases in the tissues. There was a tendency to a summation effect when the percentages of both gases were increased in inspired air; this indicated a possible advantage of the combination of these gases for therapeutic use.

The direction of the changes in the gas tensions in the tissues follows closely the changes in alveolar air and the corresponding changes in arterial blood during alterations of breathing and inspired air.¹

Changes in carbon dioxide tensions in the tissues correspond fairly well in degree as well as in direction; but there is a remarkable difference in the degree of change in oxygen tension between alveolar air and tissues when high percentages of oxygen are breathed, and to a less extent in forced breathing. Table II shows that alveolar oxygen tension was raised by 200 millimetres of mercury when a subject was breathing 50% oxygen. Arterial oxygen tension must have risen tremendously, yet the oxygen tension in the tissues which this blood entered increased by only three millimetres of mercury. Campbell⁽⁶⁾ found similar small rises in rabbits breathing more than 50% oxygen for many days. The smallness of the rise of oxygen tension in the tissues cannot be due to widespread vasoconstriction or to increased oxygen consumption by the tissues, since neither the blood pressure nor the metabolism is affected.⁽⁷⁾

This apparently remarkable phenomenon is simply explained. If normal arterial blood is exposed to an increase of oxygen tension of 200 millimetres of mercury, it can take up only approximately 1.5 cubic centimetres

of oxygen *per centum*—about one cubic centimetre in combination with haemoglobin and about 0.5 cubic centimetre in solution above normal arterial content. Since the breathing of increased percentages of oxygen does not alter oxygen consumption by the tissues, venous oxygen content will also rise not more than about 1.5 cubic centimetres *per centum*, corresponding to a rise of about 8% saturation. Observations show that there is a concurrent rise of carbon dioxide tension in the tissues, hence in venous blood, of about five millimetres of mercury. Reference to the oxygen dissociation curves of blood shows that under these conditions a rise of 8% saturation in normal venous blood corresponds to a rise of only about eight millimetres of mercury in oxygen tension.

The small rise in venous oxygen tension corresponds closely to the changes observed in the tissues, and indicates that oxygen tension in the tissues has a close quantitative relation to venous oxygen tension as was observed in the case of carbon dioxide tension.⁽⁸⁾ It follows that the average gas tensions in capillary blood must be close to those in venous blood, because it is to capillary blood that the tissues are exposed. The following considerations appear to confirm this deduction. Normally there is a drop of oxygen tension in the tissue capillaries from about 80 or 90 millimetres of mercury to 40 millimetres of mercury (from arterial to venous tensions). When 50% to 60% oxygen is breathed, this drop will be from possibly 200 to 300 millimetres of mercury to 50 millimetres of mercury. Because of the great oxygen tension gradient between capillary blood and tissues at the arterial end of the capillary, the rate of fall in capillary oxygen tension will be greatest at this site. This effect must be greatly increased by the shape of the dissociation curve of blood for oxygen, the greatest change in oxygen tension for a given change in oxygen saturation being at the arterial end of the curve. Therefore, the major part of the fall in capillary oxygen tension must occur very rapidly at the arterial end of the capillary, leaving capillary blood in a nearly venous condition through most of the length of the capillary to which the tissues are exposed. It is obvious that average capillary oxygen tension must be close to venous oxygen tension, and cannot be a mean of arterial and venous oxygen tensions, as has sometimes been supposed.

In general, alterations in breathing and in inspired air alter the gas tensions in the tissues (Tables I and II) by the changes produced in alveolar air,⁽⁹⁾ arterial blood⁽¹⁰⁾ and capillary blood. In these experimental conditions, the normal approximation of carbon dioxide tension in venous blood to that in the tissues is maintained, as is also the normal oxygen tension gradient between venous blood and the tissues.⁽¹⁰⁾ Since changes of gas tensions in the tissues in these experiments must be a reflection of changes in average capillary gas tensions, it follows that average capillary blood bears a close relation to venous blood.

Changes in Circulation.

Decrease in Local Circulation.

Complete circulatory stasis in the forearm produced by pressure around the arm for thirty-five minutes caused increases of subcutaneous carbon dioxide tension in the forearm up to 100 millimetres of mercury and decreases of oxygen tension down to, but not below, four millimetres of mercury.

Injections of adrenaline (0.02 cubic centimetre of 1:1,000 adrenaline hydrochloride solution per kilogram of body weight) into gas depots in rabbits usually caused a rise of carbon dioxide tension and a fall of oxygen tension in that depot, especially in the peritoneal cavity. This local effect is probably due to vasoconstriction. Campbell⁽⁴⁾ found similar changes in the tissues following the injection of adrenaline.

Increase in Local Circulation.

Histamine (0.02 to 0.1 milligramme per kilogram of body weight) injection into gas depots in rabbits caused slight and variable effects.

Initial injections of nitrogen under the skin or into the peritoneal cavity cause a rise of oxygen tension up to

¹ The results of experiments shown in Tables I and II should be compared with the results of similar experiments by Haldane and Priestley⁽¹²⁾ (Figures XXIII, XXIV and XXVI, and the tables on pages 22, 23 and 62).

about 50 or 60 millimetres of mercury in rabbits and up to 75 millimetres of mercury in human subcutaneous tissues. Campbell⁽⁶⁾ explained this reaction as a sterile hyperæmia. Such great increases in tissue oxygen tension above normal can be accounted for only by a great opening-up of the capillary network, the capillaries being flooded with blood that is nearly arterial in character. As noted by SeEVERS,⁽¹³⁾ the carbon dioxide tension in the tissues is lower than normal while the oxygen tension is raised, the low carbon dioxide tension corresponding to that of arterial blood. The extent of the gas tension changes suggests that the presence of gas must act directly on the capillaries, causing vasodilatation.

The induction of acute cutaneous hyperæmia by sunburn over the site of a gas depot caused no change in gas tensions in the depot. This indicates that the effect of hyperæmia is strictly limited to the tissue concerned, since cutaneous hyperæmia did not affect the deeper subcutaneous tissues.

Increase in General Circulation.

Various drugs credited with action on the circulation or other functions when administered to rabbits in "therapeutic" doses (on a comparative weight basis) were found to have remarkably little effect on the gas tensions in the tissues. Frequently, no obvious changes occurred until poisonous doses were used. The effect of such poisonous doses cannot be regarded as a true indication of the action of a drug, since secondary effects are produced.

Campbell⁽⁷⁾ found that caffeine, as a cardiac stimulant, caused a fall in carbon dioxide tension and a rise in oxygen tension in the tissues. An intravenous injection of caffeine (four milligrammes per kilogram of body weight) into a rabbit in this series caused similar changes, but only of two or three millimetres of mercury. Similar effects were noted when adrenaline was injected at a distance from the tissue under observation, in contradistinction to the local effects of this drug previously mentioned. These effects are probably due to stimulation of the general circulation, although metabolic changes also may have occurred.

The effect of a decrease in general circulation has not been studied in normal subjects. Campbell⁽⁸⁾ reported a great rise in carbon dioxide tension and a fall in oxygen tension in the tissues of a rabbit in a collapsed state following a large dose of histamine, probably due to general circulatory stasis.

Most of the experiments on changes in circulation are unsatisfactory because of the indirect methods used; but there are good indications that any increase in circulation, either local or general, will cause a fall in carbon dioxide tension and a rise in oxygen tension in the tissues due to similar changes in capillary blood. Decrease in circulation will cause the opposite effects.

It should be noted that in the experiments on respiration and circulation, the stimuli were applied to the respiratory cycle, the tissues being affected secondarily, whereas in physiological processes the stimuli arise from, or on behalf of, the tissues, and the respiratory cycle is a compensatory mechanism. The experiments show, however, how great a part the respiratory cycle can play in the regulation of gas tensions in the tissues.

Changes in Temperature.

Campbell⁽⁹⁾ found that exposure of rabbits to warm atmospheres caused a rise of carbon dioxide tension in the tissues when there was no appreciable rise in rectal temperature; but when the rectal temperature rose⁽⁷⁾ the carbon dioxide tension in the tissues fell, with a slight rise of peritoneal oxygen tension and no change in subcutaneous oxygen tension. When, however, heat was applied to one end of a rabbit and cold to the other end, there was no difference in the carbon dioxide tension.⁽¹⁰⁾ The rise in carbon dioxide tension in the tissues was ascribed to increased metabolism and cutaneous vasodilatation, with a slowing of cutaneous circulation. The fall in carbon dioxide tension was explained by hyperpnea and the rise in oxygen tension by vasodilatation. Schott⁽¹²⁾

found that immersion of rabbits in hot baths caused a fall of carbon dioxide tension in the tissues, which he explained by hyperpnea (after Campbell). The effect on oxygen tension was variable according to whether plain or effervescent carbon dioxide baths were used. Rises in oxygen tension in the tissues were explained by vasodilatation causing an increase in local circulation rate, although Campbell assumed that vasodilatation caused a slowing of circulation. It is obvious that when changes in metabolism, respiration and local and general circulation are coexistent, any combination of changes in gas tensions in the tissues may be explained with great ease.

Criticism has been made previously of the methods of Bazett and Sribyatta,⁽¹¹⁾ who found that an increase or decrease of temperature above or below 22° C. caused an increase in the subcutaneous tensions of both carbon dioxide and oxygen in the human forearm, dependent on metabolic changes. The results require confirmation.

In the present investigations many experiments were made on rabbits and human subjects covering changes in local and general temperature. Gas tensions in the tissues were found to be remarkably stable during the experiments and the slight changes noted were variable. Two experiments are worthy of note: in one, a rabbit was left in a refrigerator at 10° C. for six hours in a space too confined for exercise. No appreciable change in subcutaneous or peritoneal gas tensions were noted, nor in rectal temperature. Another rabbit was exposed to an atmosphere of about 40° C. for two hours, at the end of which time the rectal temperature had risen by 4° C. and the animal was acutely dyspnoeic and nearly collapsed. No changes in subcutaneous or peritoneal gas tensions of more than three millimetres of mercury were noted.

No quantitative relations between changes in temperature and in gas tensions in the tissues could be established, and only a few general qualitative relations. A general tendency to a rise of subcutaneous carbon dioxide tension was noted with increased temperature, local or general, until the rectal temperature rose appreciably, when the subcutaneous and peritoneal carbon dioxide tensions usually fell. The application of cold frequently caused a fall in subcutaneous carbon dioxide tension. Usually after the withdrawal of applied heat, especially when there was a rise in rectal temperature, a fall in carbon dioxide tension and a rise in oxygen tension in the tissues occurred, irrespective of the changes noted while heat was applied. Reactionary changes after the application of cold were rarely observed.

The interpretation of the effects of changes in temperature is difficult because of the interplay of the various factors already mentioned, which no doubt account for the variabilities noted. The relative stability of gas tensions is due obviously to a balance between the variable factors of metabolism, respiration and circulation. When human skin is rendered acutely hyperæmic by the application of heat, it is remarkable that the gas tensions in subcutaneous tissues do not become markedly arterial in character. Often the reverse change has been noted. Possibly the hyperæmia is strictly localized to cutaneous tissues, and does not extend to the deeper subcutaneous tissues as mentioned in a previous experiment on the effect of sunburn hyperæmia. Apparently in the deeper tissues the effect of increased metabolism predominates, and such hyperæmia as may occur in these deeper tissues is secondary to the rise in metabolism.

The Effects of Food.

Campbell⁽¹³⁾ found that food produced no change in the subcutaneous carbon dioxide tension in a cat. I have confirmed this finding for both carbon dioxide and oxygen tensions in subcutaneous and peritoneal tissues of rabbits and in the subcutaneous tissues of a human subject in repeated experiments over several hours.

The Effects of Fear and Excitement.

Several observations were made on a subcutaneous gas depot in a rabbit which showed persistent apprehension to handling. Successive samples showed pronounced rises in carbon dioxide tension and smaller rises in oxygen

tension, although there was practically no struggling. Probably a rise in metabolism was the main factor responsible for the changes noted. The observations indicate the possibility of alterations of gas tensions in the tissues by psychic changes, probably by way of metabolic changes. Such factors must be avoided in sampling by experience on the part of the subject and operator.

Changes in Metabolism.

Sleep, Basal Metabolic State and Moderate Activity.

In three experiments on a human subject estimations were made of gas tensions in the tissues and in alveolar air and of venous carbon dioxide tension directly after sleep and in subsequent states of basal metabolism and of moderate sedentary activity in the laboratory. No appreciable changes were found; this indicated that changes, if any, caused by these conditions are slight.

Exercise.

Campbell⁽⁶⁾⁽⁷⁾⁽⁸⁾ found that during exercise there was in rabbits a rise of carbon dioxide tension and a fall of oxygen tension in the tissues. After exercise the gas tensions not only returned to normal but overshot the mark considerably. Subject to considerable individual variations, similar general tendencies were noted in rabbits in the present series. The reactionary fall of carbon dioxide tension and, especially in the peritoneal cavity, the rise of oxygen tension in the tissues were the most constant features. These reactionary changes lasted two or three hours after five or ten minutes' exercise, and were usually greater than the primary changes, which varied considerably (between three and fifteen millimetres of mercury).

The effects of walking, running and ergometer exercise on the gas tensions in subcutaneous tissues of a dog and a human subject for periods up to thirty-five minutes were less definite than the observations on rabbits. Little change was usually observed, and generally the changes were in the opposite direction to those noted in rabbits—that is, there was a fall in carbon dioxide tension and a rise (or no change) in oxygen tension during exercise with a reversal of these effects in the recovery period. Variations of these effects were observed in some experiments, and no reliable observations on human tissues showed change in gas tensions greater than four or five millimetres of mercury.

Attempts were made to form gas depots in rabbits directly in contact with muscles, but the results were unsatisfactory anatomically.

Changes in gas tensions during exercise in distant tissues, such as subcutaneous and peritoneal tissues, bear no direct relation to the gas tension changes occurring in muscle. These distant tissues are subjected indirectly to alterations in respiration, local and general circulation, metabolism, temperature, hormonal influences and hydrogen ion concentrations. All these factors will tend to alter the gas tensions in distant tissues, which will thus be the products of many factors. It is not surprising, therefore, that considerable variability of response is possible. The interpretation of observed results is conjectural. Campbell laid stress on acidosis in exercise, having observed⁽⁷⁾ that intravenous injection of acid-producing substances caused a fall of carbon dioxide tension and a rise of oxygen tension in the tissues. However, in the present investigations, it was observed that the intravenous injection of 10 cubic centimetres of 2% lactic acid solution in rabbits caused only slight and variable effects. It is probable that the major effects noted during exercise were due to local changes in circulation in the tissues under observation, together with changes in the gas tensions of arterial blood, following changes in alveolar air. The effect of exercise in raising the subcutaneous carbon dioxide tension in a rabbit was simulated by the intraperitoneal injection of 400 cubic centimetres of carbon dioxide. It is highly probable that in this experiment, as in exercise, the carbon dioxide tension was raised successively in the tissue concerned (peritoneum or muscles), thence in the tissue capillaries, venous blood, alveolar air, arterial blood, subcutaneous

capillaries and subcutaneous tissues. Gas tensions in the tissues show a variability of response and a general stability to exercise.

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A REVIEW OF THE LITERATURE CONCERNING HÆMORRHAGE IN OBSTRUCTIVE JAUNDICE; THE SIGNIFICANCE OF PROTHROMBIN AND OF VITAMIN K THERAPY.

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A CONSIDERABLE number of experimental and clinical observations made in the past few years have led to a fuller understanding of the factors concerned in the development of the tendency of jaundiced patients to bleed, and to a satisfactory method of treatment of this condition. A summary of the literature is given in which are described tests for prothrombin activity and experimental work concerned with the discovery of vitamin K and its clinical application.

Physiology of Coagulation.

The mechanism of the clotting of blood is not fully understood, and physiologists are at variance even as to the fundamental factors involved in this process. Coagulation of the blood appears to take place in two stages: first, the formation of thrombin from its precursors, prothrombin, calcium and tissue extract, and secondly, the action of thrombin in the conversion of fibrinogen into fibrin. Theories as to the precise nature of the essential constituents of these processes and the part they may play in colloidal, enzymal or physico-chemical reactions are discussed in the reviews of Eagle (1937), of Howell (1935) and of Wohlich (1929). The last author refers to over nine hundred papers.

Prothrombin appears to be a plasma protein of the globulin fraction, possibly formed in the liver or from the platelets. Calcium ions normally take part in the activation of prothrombin probably as a catalyst and not as a constituent of the product thrombin. The tissue factor, variously termed thromboplastin, thrombokinasase or zymoplastic substance, is probably a cephalin protein compound formed during the disintegration of platelets or during tissue damage. Morawitz suggests that it acts as an enzyme during the formation of thrombin from prothrombin. Bordet postulates direct union with prothrombin; Fischer includes calcium in this compound; and Howell holds that it unites with or neutralizes the heparin (antiprothrombin) of the prothrombin-antiprothrombin complex, thus setting free prothrombin for the formation of thrombin. Mills suggests that it unites with calcium and fibrinogen to form fibrin, prothrombin and thrombin not being necessary. This last theory is controverted by many authors, including Davidson (1937).

The action of thrombin is generally regarded as that of a hydrolytic enzyme. Fibrinogen is a protein of the globulin fraction, formed mainly in the liver; activated by thrombin it forms insoluble fibrin, precipitated as "needles and threads" entangling platelets and corpuscles.

Platelets, as well as being a potent source of the thromboplastic substance, are thought by many authors, Howell especially, to be a source of prothrombin. Tocantins (1936) has shown their importance in the strength and contraction of the clot. The normal fluidity of the blood is assumed by Howell to be due to the presence of heparin, which in combination with prothrombin prevents it from being activated. It is probably a chondroitin-sulphuric acid, present throughout the body, but predominantly in the liver, lungs and muscles.

Consideration of Coagulation Factors in Obstructive Jaundice.

The explanation of the defective coagulability of the blood in obstructive jaundice may be expected to lie in the deficiency or modification of one or more of the factors taking part in normal coagulation.

Calcium.

The addition of bile acids to blood *in vitro* renders it incoagulable, but only when the acids are present in concentrations far in excess of those found in the body. King and Stewart (1909) found an increase in the serum calcium content in jaundice, and suggested that the bile pigments were rendered less toxic by combination with calcium. This explanation was given for the negative calcium balance found in obstructive jaundice by King, Bigelow and Pearce (1911).

The administration of calcium to jaundiced patients appears to date from Mayo Robson (1894), who obtained the idea from the experiments of Wright (1891), in which the administration of calcium chloride to dogs by mouth or intravenously shortened the coagulation time of the blood. Lee and Vincent (1915) tied and cut the common bile duct of a dog to produce obstructive jaundice and then repeatedly estimated the coagulation time of the animal's blood. Prolongation reached its maximum after about five weeks. The administration of calcium by mouth seemed to diminish the coagulation time, and the intravenous administration of calcium lactate also seemed temporarily to shorten the clotting time. Lee and Vincent suggested that the tendency to bleed was due to deficiency of the available calcium of the blood, possibly by reason of the formation of a loose combination with the bile pigments. Walters (1921) and Walters and Bowler (1924) claim excellent results from the intravenous injection of five to ten cubic centimetres of a 10% solution of calcium chloride on three successive days before operation. The coagulation time was reduced and the bile pigments were rendered "less toxic". It is to be noted that the response to the calcium *in vitro* test of Lee and Vincent (1915) exceeded the normal coagulation time in most cases. Emerson (1929) found that calcium chloride had no effect on the toxicity of bile in an otherwise normal animal.

Gunther and Greenberg (1930) and Ivy (1930) review the evidence concerning the blood calcium level in jaundice. The earlier methods of estimation of calcium, such as those of King and Stewart (1909) are criticized. Gunther and Greenberg found no deficiency in the diffusible calcium of the blood serum of patients with icteric indices between 17.5 and 200, whether abnormal bleeding was present or not. Calcium deficiency is also denied by Snell, Green and Rowntree (1925), Snell and Greene (1930), Zimmermann (1927) and Ravdin (1929, 1930). While Cantarow *et alii* (1926, 1927) found but little variation in the blood calcium level in jaundice, they thought that there was a functional deficiency and claimed benefit for the exhibition of parathyroid extracts. Ravdin (1937) instances normal clotting times with a serum calcium content of 5.2 milligrammes per centum in parathyroid tetany, and in hyperparathyroidism with a content of 15.4 milligrammes per centum, and Crane and Sanford (1937) found no significant changes in the coagulation time with calcium concentrations between 5 and 20 milligrammes per centum. Wangenstein (1928), while noting numerous instances in which calcium and parathyroid extracts shortened the coagulation times with and without the addition of calcium, stated that other treatment, including injections of gelatin, of sodium chloride, of glucose or serum, of platelet extracts, or irradiation of portion of the body, would shorten the *in vitro* coagulation time of the blood.

One thus feels that while there is an altered calcium balance, as evidenced by osteoporosis and increased excretion of calcium in the faeces (King, Bigelow and Pearce, 1911; Wangenstein, 1929; Hawkins and Whipple, 1935), calcium therapy has not solved the problem of bleeding in jaundice.

Fibrinogen.

The estimation of the blood fibrinogen level has been carried out by many investigators (Whipple, 1911, 1922; Smith, Warner and Brinkous, 1937; Rush, 1940), and while diminution is noted in severe liver damage, the level is so nearly normal in most cases of hæmorrhage in obstructive jaundice that it cannot be regarded as an important factor in this condition.

Prothrombin.

Studies of Lewisohn (1931) and of Bancroft, Kugelmass and Stanley-Brown (1929) have indicated that the bleeding tendency in jaundiced patients may be explained by the amount of prothrombin in the plasma. Other factors, such as platelets, antithrombin and antiprothrombin, have been found at normal levels or cannot be shown to vary constantly.

The approach to prothrombin deficiency and its treatment has been made from three directions: first, experiments concerning a hæmorrhagic disease of cattle fed on improperly cured clover; secondly, the bleeding tendency which developed in laboratory animals with biliary fistula; and thirdly, a hæmorrhagic disease of chicks of dietary origin.

Roderick (1931) showed quite definitely that the feeding of damaged sweet-clover hay to cattle resulted in a reduction of the prothrombin content of the blood proportional to the delay which developed in the coagulation of the blood. Further reduction in prothrombin content was accompanied by hæmorrhage, spontaneous or from trauma. A precipitate of the prothrombin fraction, obtained by the method of Howell (1911), was shown to be active for prothrombin when made from the plasma of normal animals, but inactive when made from the diseased animals. The contents of heparin, antithrombin and platelets were shown to be within normal limits. Treatment by transfusion of normal blood caused immediate improvement, and removal of the spoiled clover from the diet gave relief in a few weeks.

Quick (1937) confirmed Roderick's results and showed that the addition of 5% of alfalfa to the diet, even when spoiled clover hay was continued, effected a cure. He suggested that the hæmorrhagic tendency in obstructive jaundice might be due to deficiency of the factor contained in alfalfa.

Meanwhile Hawkins and Whipple (1935) reported a tendency to spontaneous bleeding occurring along with other abnormalities in dogs deprived of bile by biliary fistula. They found that after three to five months' total deprivation of bile the clotting time lengthened, and finally spontaneous bleedings from mucous membranes and prolonged bleeding from sites of minor trauma occurred. Hawkins and Brinkhous (1936) showed that there was no bleeding if the animals were given adequate amounts of bile, but that if they were given inadequate amounts or entirely deprived of bile, bleeding occurred. This was abolished in two or three weeks if bile feeding was resumed. They noted that transfusion gave temporary improvement. The only significant change in the constituents of the blood appeared to be a profound reduction in the amount of prothrombin in the plasma, which they estimated by the method developed by Warner, Brinkhous and Smith (1936). The fibrinogen, antithrombin and serum calcium contents were shown to vary insufficiently to alter the clotting. There is a wide margin of safety, the tendency to bleed constantly coming into evidence only when the prothrombin level is below 20% of normal.

Smith, Warner and Brinkhous (1937) modified their prothrombin titration method and showed that the bleeding tendency in dogs with liver injury produced by chloroform poisoning was due to prothrombin deficiency, although in severe cases a lowered fibrinogen level contributed to the delayed coagulation of the blood. Warner, Brinkhous and Smith (1937) estimated the prothrombin level in many jaundiced patients as 50% or more of normal, these patients showing no tendency to bleed. Below 35% bleeding often occurred, spontaneously, at operation or later from the wound. They noted the cessation of bleeding with a rise of prothrombin level brought about by transfusion, restoration of bile to the intestine by relief of obstruction, or the giving of bile by mouth. These authors showed that there was a more rapid rise in prothrombin level when substances rich in vitamin K as well as bile were added to the diet. Smith, Warner, Brinkhous and Seegers (1938) found a similar more rapid rise in the prothrombin level of the plasma of dogs with biliary fistulae when vitamin K concentrates were added to bile feeding. The fact that the exclusion of bile from the intestine is followed at varying intervals in different cases by the development of a hæmorrhagic tendency indicates the existence of additional factors. Greaves and Schmidt (1938) produced low prothrombin levels and prolonged coagulation times in rats with bile fistulae, but not in normal rats, by feeding them on a diet low in fat and by excluding bile from the intestine by ligation of the bile duct. The restoration of prothrombin to normal levels was accomplished by the administration of massive doses of vitamin K (without bile salts), or of bile, or by restoration of the bile flow to the intestines. The part played by the absence of bile from the intestine is stressed by Cohn and Schmidt (1939), who found that de-oxycholic acid was necessary to ensure absorption of the anti-hæmorrhagic factor when it is given orally to rats with bile fistulae, and also by Brinkhous, Smith and Warner (1938), who report successful rises in prothrombin level obtained by the administration of bile and vitamin K to patients with obstructive jaundice. McNealy, Shapiro and Melnick (1935) report the results in a series of over 800 cases of jaundice due to various causes—cholelithiasis, cholecystitis, stone in the common duct, cirrhosis of the liver, catarrhal jaundice, carcinoma of the liver and of the bile ducts. In this series a proportion of the patients with prolonged bleeding times, by means of the method of Ivy (1935), were given "Viosterol", and when the stools were acholic, bile salts also. In comparison with those with prolonged bleeding times who were not given "Viosterol", these patients in the main showed a shortening of the bleeding time and the clinical course at operation and subsequently was much more satisfactory. It is probable that the diminution of the bleeding tendency was due to the absorption of vitamin K following the exhibition of bile salts. In 1933 Wright demonstrated the value of bile salts in aiding the general digestion and

absorption of fats. He was probably the first to advocate their use in obstructive jaundice.

The tendency to the occurrence of bleeding as a result of a dietary deficiency was noted by McFarlane, Graham and Richardson (1931) in chicks whose source of protein was meat or white fish extracted with ether. Dam (1929, 1930) and Dam and Schönheyder (1934) described a disease similar to scurvy occurring in chicks receiving an artificial diet. The condition was relieved by the addition of cereals. Dam (1935) showed that the addition of extracts of known vitamins A, D, E and C was not effective, but that the necessary factor was present in many seeds, cereals, vegetables and animal organs, the most potent sources being hemp seed, tomatoes, lucerne (alfalfa) and hog's liver. He suggested the name vitamin K (*Koagulations-vitamin*).

Schönheyder (1935, 1936) described a method of assay of the vitamin based on the measurement of clotting time. Dam and his co-workers (1936, 1937, 1938) estimated the potency of various foodstuffs; cabbage, spinach and lucerne ranked higher with about 250 units per gramme when prepared in tablet form and assayed by Schönheyder's method. They also prepared by various fractionation, absorption and distillation methods concentrations containing up to several hundred thousands units per gramme. Although light appeared essential for the synthesis of the vitamin, withered leaves contained as much vitamin in the yellow as in the green portions, and the activity was not destroyed by the removal of the chlorophyll. While chicks, ducklings and young geese readily developed the hæmorrhagic tendency, rats, guinea-pigs and dogs were fed on a diet free from vitamin K for a long time without any signs of the disease appearing. As is shown later, it is probable that in these latter animals the vitamin is synthesized, perhaps by intestinal bacteria. Active and inactive preparations respectively were obtained from the plasma of normal chicks and K-avitaminous chicks, the methods used for the precipitation of prothrombin being those described by Howell (1911) and Mellanby (1930). That from normal chicks was still active after removal of the lipids by acetone and ether. While vitamin K itself did not accelerate clotting *in vitro*, prothrombin appeared to contain vitamin K.

Other workers, notably Almquist (1936, 1937, 1938) and Almquist and Stokstad (1935, 1936), have obtained results similar to those of Dam and his co-workers. Almquist, Pentler and Mecchi (1936) have shown that the anti-hæmorrhagic factor in fish meal is removed by ether extraction, but if the meal that is free of vitamin K is then allowed to putrefy its activity is restored. An organism was isolated in several instances which proved to be a rich source of vitamin K. Dried bacteria of some species showed five to eight times the anti-hæmorrhagic activity of dried alfalfa. The demonstration by Greaves (1939) of vitamin K in the faeces of rats receiving a diet free from vitamin K suggests that vitamin K is synthesized by intestinal bacteria. Quick and Grossmann (1939) thus explain the fluctuations in prothrombin level in the first few days of post-natal life; until an intestinal flora is established, vitamin K is not formed to aid in the production of thrombin. Low prothrombin levels in infants have been reported by Quick and Grossmann; Owen, Hoffman, Ziffren and Smith (1939); Brinkhous, Smith and Warner (1939); Waddell *et alii* (1939); Rush (1940); Norris and Rush (1940).

Following their investigations on bacteria isolated from putrefying fish meal, phthiocol (2-methyl-3 hydroxy-1, 4 naphthoquinone), which was isolated from the tubercle bacillus in 1933 by Anderson and Newman and later synthesized, was found by Almquist and Klose (1939) to have a high anti-hæmorrhagic activity. The nucleus, 2-methyl-1, 4 naphthoquinone, also has high anti-hæmorrhagic activity. While potent products have been prepared by various groups of workers, it fell to Binkley and his co-workers (1939) to announce the isolation of what appears to be pure vitamin K. Two similar but separate compounds can be obtained, K_1 from alfalfa and K_2 from fish meal. The vitamin is an unstable lemon-yellow oil, very sensitive to light and to alkali (MacCorquodale *et*

alii, 1939). The formula is given as $C_{21}H_{20}O_6$, or 2-methyl-3-phytyl-1, 4 naphthoquinone. Almquist and Klose, among others, find that 2-methyl-1, 4 naphthoquinone has two to three times the antihæmorrhagic activity of the pure vitamin K_1 , the addition of a phetyl side chain in the 3 position apparently detracting from the activity of the nucleus.

Various methods of assay are given, by Almquist and Klose (1939), Thayer *et alii* (1939), Ansbacher (1939). Most authors agree with the suggestion of Thayer and his co-workers that one unit should be defined as the antihæmorrhagic activity of one microgramme of pure 2-methyl-1, 4 naphthoquinone. This compound is less difficult and less expensive to synthesize than vitamin K_1 , and possesses greater activity. The various properties of vitamin K and allied compounds and their synthesis are detailed in a series of communications from several laboratories, published in *The Journal of the American Chemical Society*.

Clinical Results.

So rapid has been the discovery of concentrates and compounds of increasing antihæmorrhagic properties that each substance has been tested only in a small number of patients. Good results with substances rich in vitamin K and with concentrates administered by mouth together with bile salts have been claimed by many authors, including Dam and Glavind (1938); Butt, Snell and Osterberg (1938); Warner, Brinkhous and Smith (1938); Walters (1938); Illingworth (1939); Scanlon *et alii* (1939); Stewart (1939).

Intramuscular administration of phthiocol has met with more moderate success (Butt, Snell and Osterberg, 1939); but Macfie *et alii* (1939) are more optimistic concerning the use of 2-methyl-1, 4 naphthoquinone. Ten milligrammes were injected intramuscularly on the first day and five to ten milligrammes on subsequent days till the hypoprothrombinæmia was relieved.

Similarly, rapid response to vitamin K therapy in the hypoprothrombinæmic states of the new-born is reported by Waddell and Guerry (1939); Dam, Tage-Hansen and Plum (1939); Nygaard (quoted by Macfie) and Helman and Shettles, Shettles *et alii* (1939). The last mentioned have shown the value of administering vitamin K to mothers prior to delivery, the prothrombin level of the infants thereby often being increased threefold. Their results have been confirmed by MacPherson *et alii* (1940).

The beneficial effect of blood transfusion in jaundice is well known and widely advocated (Keith, 1939; Judd, Snell and Hoerner, 1930; Walters, 1938). It is probable that this is due to the presence of prothrombin in the donor's blood (Lord *et alii*, 1939). Roderick noted improvement in the condition of cattle suffering from the hæmorrhagic sweet clover disease following transfusion. Transfusion is of great value in *melena neonatorum*.

With the development of blood banks the question arises as to the prothrombin content of blood stored for some time and the usefulness of such blood for jaundiced patients. Rhoads and Panzer (1939) from their investigations think that blood a week or more in the bank would probably be useless in the treatment of prothrombin deficiency as it occurs in obstructive jaundice. Blood three days in the bank would be of slight value, but very inferior to fresh blood. Experiments carried out in this hospital confirm their views.

Estimation of Prothrombin Content.

A simple clinical test of general application is that described by Ziffren (1939). One cubic centimetre of freshly drawn venous blood is added to 0.1 cubic centimetre of thromboplastin solution in a test tube of a capacity of three cubic centimetres. The tube is inverted once and then tilted every few seconds, and the time taken for the formation of a clot is noted. A similar method was suggested by Quick (1935).

Where the sample of blood has been rendered incoagulable by the precipitation of calcium salts, Quick's method (1938) or a modification is most suitable; 0.1 cubic centimetre of plasma and 0.1 cubic centimetre of

thromboplastin solution are mixed and 0.1 cubic centimetre of a 1% solution of calcium chloride is added, and the time taken for a clot to form is recorded.

These tests measure the sum of several variables, being an expression of the tendency to bleed, and are not an accurate estimation of prothrombin. In Quick's test the number of variables present during normal clotting is reduced by two; adequate calcium and thromboplastin are provided. Warner, Brinkhous and Smith (1936) developed a two-stage titration method in which all the prothrombin was first converted into thrombin before clotting was brought about by the addition of adequate fibrinogen.

A comparison of the tests of Ziffren and Quick with the two-stage titration method reveals that when by the last test prothrombin is estimated at 50% of normal the simpler tests may give normal values. This again suggests that other factors exist which may compensate for any prothrombin deficiency, and is further borne out by the experiments of Warner, Brinkhous and Smith (1939), in which the rate of conversion of prothrombin into thrombin in the dog and rabbit is found to be much faster than that in man and guinea-pig. Quick (1938) has ascribed to a quantitative difference in prothrombin variations in the "prothrombin time" of rabbit, dog and cat blood as compared with that of human blood. Warner, Brinkhous and Smith (1939) find but little difference in the total amounts of prothrombin in human and rabbit blood. It is interesting to note that the experiments of Lee and Vincent (1914) revealed a much slower rate of formation of thrombin in human than in rabbit blood.

In brief, the two-stage titration method is carried out as follows:

Fifteen cubic centimetres of blood are collected in isotonic oxalate solution and the plasma is obtained by centrifugation in a hematocrit. Thirty drops of plasma are defibrinated by the addition of three drops of thrombin. The resulting fluid is diluted 1 in 20, 1 in 30, and 1 in 40 with oxalated saline solution, and each dilution is tested for prothrombin by the addition of equal parts of saline solution, calcium chloride, and tissue extract; incubation is carried out for a suitable period and finally a similar amount of fibrinogen is added. The clotting time is then measured with a stop watch. The final dilution of the plasma with which a clotting time of fifteen to eighteen seconds is obtained, is the prothrombin unit concentration. If, for example, the final dilution of the plasma at the time of clotting is 1 in 300, the plasma contains 300 units of prothrombin.

The time taken in the preparation of the reagents, especially fibrinogen and thrombin, precludes the use of this test in clinical cases; but it remains the most accurate estimate of the plasma prothrombin content which has so far been elaborated.

The test described by Ziffren is most suitable for clinical use, although in our experience at this hospital thromboplastin prepared by Quick's method was much more stable and gave less variability in the results. Quick's test has been used in this hospital to estimate the prothrombin levels in stored blood.

Where facilities are not available for the performance of these estimations the simpler procedures of the determination of the Ivy bleeding time and the serum volume index of Boyce may indicate a tendency to bleed. Ferguson *et alii* have compared the three tests in cases with jaundice or biliary fistula.

Preparation of Thromboplastin.

The method for the preparation of thromboplastin recommended at the hospital is in the main that described by Quick (1938).

Dehydrated brain (0.3 gramme) is shaken with five cubic centimetres of normal (0.89%) saline solution and incubated at 45° C. for twelve minutes. Brain may be dehydrated as follows. After removal of the blood vessels and the meninges about 150 grammes of human or animal brain are macerated in a mortar and extracted with acetone. This is poured off and fresh acetone is added, the process being repeated until a fine granular powder is obtained. After having been dried at 37° C. the powder is stored in a stoppered bottle in an ice chest.

Summary.

In a review of the vast literature on this subject the following points emerge:

1. No deficiency of calcium in the blood of jaundiced patients has been proven, and the therapeutic effect claimed for the administration of calcium is not fully substantiated.
2. A deficiency in the prothrombin content of the blood plasma may occur as a result of inadequate vitamin K in the diet of such animals as chicks, ducklings and young geese; but mammals such as guinea-pigs, rats, dogs and presumably human beings, can live indefinitely on a diet free from vitamin K without developing a hemorrhagic tendency due to prothrombin deficiency. It is to be noted, however, that Kark and Lozner (1939) have reported four cases of hypoprothrombinemia in man which appear to be due to dietary deficiency.
3. The prothrombin level of the blood of newly born babies appears to be precariously low until an intestinal flora is established which synthesizes the vitamin.
4. In rats, dogs and human beings exclusion of bile from the intestine prevents absorption of the vitamin and results in prothrombin deficiency after a varying period of time. Other varieties of steatorrhea, such as sprue or celiac disease, intestinal fistula, stenosis and granulomatosis, may similarly bring about deficient absorption of the vitamin.
5. Diminution of functional liver tissue, whether from hepatectomy, cirrhosis, toxic degeneration or carcinomatosis, may cause a lowering of the prothrombin content of the blood.
6. In obstructive jaundice both liver damage and absence of bile from the intestine may play a part. Prothrombin deficiency may be readily demonstrated by simple clinical tests. Effective treatment consists of the administration of bile salts by mouth and the addition of foods or concentrates rich in vitamin K. Preparations of the actual vitamin or of closely related substances are more potent. Intramuscular injections of the latter produce a rapid response and are recommended by recent writers.
7. Transfusion of fresh blood is a good method of temporarily raising the prothrombin level of the blood.

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Reports of Cases.

COMPLICATIONS OF LABOUR IN A CRETIN.

By MARY C. DE GARIS.

(From the Maternity Unit of the Geelong Hospital, Geelong.)

Clinical Record.

A SINGLE woman, aged twenty-two years, a *primipara*, was admitted to hospital on July 20, 1939, with albuminuria and

oedema. She had had a miscarriage by hysterotomy in the previous year. The patient was a cretin, who had received no treatment until the age of five years; since then she had had thyroid extract regularly and throughout the pregnancy. The menstrual periods had been painful and had occurred regularly every twenty-four days; the patient had some caries and some artificial teeth, and she had a fair diet with a large amount of milk. She had twice attended the antenatal clinic—on the first occasion when she was four and a half months pregnant.

A trial of labour was decided upon and the patient was delivered by forceps on September 2, 1939, as a precaution against rupture of the hysterotomy scar, although it had given no signs of trouble. The first stage of labour lasted for seventeen and a half hours, and was preceded by two days of niggling pain; the second stage lasted three hours and ten minutes, and the third stage lasted three-quarters of an hour. During the third stage a little pressure was used. There was some post-partum hemorrhage. On the fifth day the patient's temperature rose to 100.8° F., and for several days it was between 99° and 100° F. The baby was a female, which weighed nine pounds five ounces at birth and nine pounds three ounces when the patient was discharged from hospital on the eighteenth day. The patient was able to breast-feed the baby satisfactorily at first.

The baby required some restorative measures at birth, but did well afterwards. For the first three days she was given one-tenth of a grain of thyroid extract; but as her eyes then became staring, the administration was discontinued. An X-ray examination of her wrist before her discharge from hospital revealed two carpal centres of ossification. I thought that, far from being subthyroidal, she tended to be hyperthyroidal. Seen fourteen months later, she was walking, had some words and looked very intelligent.

MEASLES AND PNEUMONIA COMPLICATED BY THE TOXIC EFFECTS OF SULPHAPYRIDINE.

By MARY C. PUCKEY,

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South Australia.*

Clinical Record.

J.P., aged twenty-four years, a nurse trained in a general hospital, was admitted to the Metropolitan Infectious Diseases Hospital, Northfield, on August 15, 1940, suffering from measles and bronchopneumonia. The history given was one of pneumonia since August 7, the measles rash having appeared on August 14. Before her admission to hospital, the patient had received 36 grammes of sulphapyridine in nine days, and a dose of 0.5 gramme every four hours was given after her admission to hospital for 11 doses; a total dosage of 41.5 grammes was given in ten days. The drug was then discontinued, as the patient had received a large dose and was showing signs of toxicosis. She was cyanosed and complained of pain over the liver and swelling of the hands. During this time the temperature varied between 100° and 104.2° F., rising to 104.6° F. after the withdrawal of the drug.

On her admission to hospital the patient was obviously very ill; her face was cyanosed, a typical morbilliform rash was present on her face and trunk; slight conjunctivitis and Koplik's spots in the mouth were noticed, and general faucial inflammation was also present. The tongue was moist and cracked and there were signs of resolving consolidation at the bases of both lungs. The temperature was 102° F., the pulse rate was 100 per minute and the respirations numbered 36 per minute.

The patient's general condition did not improve, and on August 18, three days after her admission to hospital and twenty-four hours after the withdrawal of sulphapyridine, her temperature rose to 104.6° F., distinct jaundice of the sclerotics and skin was present, bile was found in the urine, and mild generalized oedema was noticed. The fluid intake and output were entirely satisfactory. The patient was now considered to be suffering from measles and bronchopneumonia complicated by the toxic effects of sulphapyridine. On August 19, calcium gluconate (10 cubic centimetres) was given intramuscularly, and five cubic centimetres were given per day for three days, a total of 25 cubic centimetres in all. At the end of that time the patient's general condition had improved, the jaundice and oedema had disappeared and her temperature was normal.

A blood count on August 17 revealed that the white cells numbered 25,000 per cubic millimetre and the hæmoglobin

value was 85%. Two days later the total number of white cells had fallen to 15,800 per cubic millimetre, and the hæmoglobin value had risen to 100%; two days later again the number of white cells had fallen to 7,600 per cubic millimetre and the hæmoglobin value remained 100%; a differential count revealed a big drop in the number of granular cells and a large proportion of old neutrophile cells. This state of affairs continued until August 28, eleven days after the original count, when the total number of white cells was 4,600 per cubic millimetre; 71% were lymphocytes, 24% were neutrophile cells, 2% were eosinophile cells and 3% were basophile cells; the hæmoglobin value was still 100%. On August 29 "Pentnucleotide" (10 cubic centimetres) was given intramuscularly twice a day for three days. At the end of that time the white cells numbered 8,787 per cubic millimetre; 35% were lymphocytes, 59% were neutrophile cells, 4% were eosinophile cells, 2% were basophile cells, and there was a general increase in the number of young granular cells. The patient's condition generally was good, and she was discharged from hospital six days later to convalesce.

Discussion.

A case of measles and bronchopneumonia complicated by the toxic effects of sulphapyridine is reported. The hepatitis, which is considered to be rare, responded to treatment with calcium gluconate. The steady fall in the number of white cells and the low percentage of granular cells responded to the administration of "Pentnucleotide". At no time were nausea and vomiting troublesome.

Acknowledgements.

I have to thank Dr. M. E. Chinner, in whose care this patient was admitted to hospital, for permission to publish this case.

Reviews.

HUMAN GENETICS.

It is unlikely that the busy medical practitioner would choose such an intricate subject as modern genetics upon which to browse in the precious time of leisure. He will find both relaxation and stimulation, however, in a careful reading of "You and Heredity".¹ In this book the author, Mr. Amram Scheinfeld (who was a journalist before his mutation to a geneticist) discourses in a highly entertaining fashion about the potentialities for good or evil which lie latent in every human gene and chromosome. Considering the fact that no less an authority than Professor J. B. S. Haldane has given the signature of his approval to the author's method of popularizing a science which should be the concern of every member of the human family, we have the assurance that at least we are being educated upon the right lines.

It would seem that a great deal of research has been carried out in this field since the rediscovery of Gregor Mendel's original work just forty years ago. One result has been that many cherished notions, and even superstitions, about conditions thought to be influenced by heredity are now proved to be entirely erroneous. But what is even more important, we are probably in a better position to appreciate the line of demarcation between unalterable qualities in an individual and those capable of higher development with the help of opportunity and environment.

In a free and easy style of expression Mr. Scheinfeld proffers a delectable feast of information on such topics as the determination of sex, musical talent and aptitude, blood grouping and doubtful paternity. There are chapters incriminating the dominant and recessive genes responsible for unsightly deformities and incapacitating diseases met with commonly enough in a medical practice. And most people will be intrigued to hear what happened to the famous Dionne quintuplets from the moment of their conception to the peak period of their acclamation by an admiring world.

This book should be acceptable to the general reader, and some day it might be helpful to social reformers and politicians when the time comes for planning a new way of life for future generations.

¹ "You and Heredity", by A. Scheinfeld, edited by J. B. S. Haldane; 1939. London: Chatto and Windus; Australia: Angus and Robertson. Demy 8vo, pp. 453, with illustrations. Price: 16s. net.

The Medical Journal of Australia

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CORONARY OCCLUSION AND EFFORT.

In a previous issue a discussion was devoted to the prognosis and rehabilitation in coronary thrombosis, and subsequently reference was made to trauma in relation to diseases of the coronary vessels. It was decided to divide the subject of trauma into two, and confusion of the heart was therefore discussed in the issue of December 21, 1940. On this occasion attention will be directed to the relationship between effort and coronary disease. In *angina pectoris* it is a common experience that an attack follows physical exertion or some unusual or excessive emotional strain; by analogy, and without either critical analysis or justification, bodily exertion has been held to be responsible for many cases of coronary occlusion. Whether this is true or not is important not only from the scientific, but from the medico-legal point of view, for we can imagine that claims for compensation might be made by workers whose coronary occlusion followed some unusual effort or strain in the course of their employment. If we set out to determine whether or not effort may have a part in the causation of coronary occlusion, we have to take many facts into consideration. The first, and perhaps the most obvious, is that the coronary arteries become occluded in persons engaged in all types of occupation, non-manual as well as manual; the condition is in fact often regarded as being very much a professional man's disease. It is therefore safe to conclude that if effort has any place at all in the aetiology, it cannot be one of major importance. As a matter of fact, the general recognition that coronary occlusion is a complicating manifestation of general arterial disease shows that a major aetiological role is not now assigned to effort. It was somewhat different not so many years ago, when coronary occlusion was looked on as a terminal complication of *angina pectoris*. This

does not imply that *angina pectoris* and coronary occlusion may not occur in the same patient. That they may do so is shown by a somewhat diffuse article published in 1933 by G. Fitzhugh and B. E. Hamilton.¹ In this paper mention is made of thirty-one patients who had "coronary occlusion or fatal angina" following directly on unaccustomed exertion, and twenty-four after unaccustomed exertion "which could also be called violent". The exertion is described and in several histories there appears the statement that the patient had a coronary occlusion. There are no details of post-mortem findings and there is no chance for the reader to determine in how many cases angina and in how many cases coronary occlusion was supposed to be responsible for death. The point at issue is whether effort *per se* can bring about the formation of a thrombus on the wall of an already diseased coronary artery. Many investigators and experienced clinicians hold that it cannot. Among Australian workers maintaining this view must be quoted S. A. Smith, who, in an article on trauma and the heart published in this journal as long ago as 1931, stated that in his opinion exertion played no part in causing or aggravating heart failure from occlusion of the coronary artery. Obviously effort may have an untoward effect on the action of a heart whose muscle is diseased, else what were the reason for the ordering of continued rest for a patient suffering, for example, from congestive cardiac failure? But this is no indication that thrombosis may be occasioned by effort. We know beyond doubt that coronary occlusion occurs in an artery that is affected by atheromatous degeneration, and we know also that this degeneration is the underlying cause of thrombosis that takes place in the vessel. The trouble is that though many men hold views similar to those expressed by S. A. Smith, they are unwilling, they lack the courage, to commit themselves. They prefer to leave the "little loophole for escape" that will be available at any later date if they should find reason to alter their views or to compromise with their beliefs. There are others, of course, who are convinced that opposite views are correct.

In our recent discussion on prognosis and rehabilitation in coronary thrombosis reference was made to an article by A. M. Masters, S. Dack and H. L. Jaffe,² and to their conclusions regarding effort and coronary occlusion. Fuller details of their contentions may now be given. These authors have been working on this subject for some years and have published several articles dealing with it. Readers to whom *Industrial Medicine* is not available will find a discussion by these same authors on the same subject in *The Journal of the American Medical Association* of August 21, 1937. After years of study these authors have collected records of many cases that they have investigated. In the article now to be discussed they have investigated 1,620 attacks of coronary occlusion. They insist on the distinction between angina and coronary insufficiency with infarction on the one hand and coronary occlusion on the other; all cases of the former group have been excluded by them. In their investigations the activities of the patient have been investigated, not only at the time of the attack, but during the preceding twenty-four hours and also the four weeks prior to the attack.

¹ *The Journal of the American Medical Association*, February 18, 1933.

² *Industrial Medicine*, July, 1940.

Fifty patients who were seeking compensation were excluded, since it was found that histories given in these circumstances were unreliable. "A comparison of the history given by the patient in the hospital soon after the attack and that given at the compensation hearing months later reveals that the former story is often entirely at variance with the latter." Of the attacks, 52.2% occurred while the patient was asleep or at rest; 21% occurred during routine activity; 15% occurred while the patient was walking at an ordinary pace, and 9% during moderate activity. Only 2% were associated with unusual activity. Masters, Dack and Jaffe point out that these figures correspond quite closely to the portion of the day spent by the majority of people in each activity mentioned. They hold that since most people spend at least 40% to 50% of the day asleep or at rest, and since 40% to 50% of attacks occurred during these states, it may reasonably be concluded that the onset of the occlusion was not influenced by the activity or lack of activity of the patient at the time. They hold that the association of occlusion with the activities of the patients just mentioned was merely incidental. They also insist that the association of unusual activity with the attack in only 2% of cases excludes effort as a factor. It may be noted in passing that seventy of their patients prior to the occurrence of occlusion had been bedridden on account of a chronic illness. There could be no question of effort in these cases. At this stage we may note that 36% of patients in their series were manual workers and labourers, 9.5% were "white collar and office workers", 8.5% were professional persons, 11% were business men, 20% were housewives, and 9.5% were "retired". These percentages, we are told, correspond to the occupational distribution in New York City.

The contentions of some workers who hold views opposed to those of Masters, Dack and Jaffe should be mentioned. E. P. Boas is among these. In a communication published in May, 1939, he admits to begin with that the preponderant opinion at present is that the association of trauma and effort with coronary occlusion is coincidental.¹ Boas thinks that one reason why many clinicians are reluctant to accept a causal relationship between effort and coronary occlusion is the fact that when an injury occurs during work the patient naturally seeks to show that the work as such was responsible for his disability. "He may wittingly or unwittingly construct a logical series of events leading up to his injury." Boas presents fourteen cases in which he holds that the association was proven, but only five involved a problem of workmen's compensation; in the others the patient had nothing to gain by ascribing his illness to an unusual effort. In reply to the last of these statements it may perhaps be pointed out that almost every patient will look for some obvious cause for an obscure and baffling illness. For example, there can scarcely be a woman with cancer of the breast who does not recall an injury to that organ. Heart conditions are in the popular mind so bound up with effort, or rather their amelioration with all freedom from effort, that no surprise will ever be expressed when a patient with a heart seizure declares that a sudden effort has been responsible. Be that as it may, in nearly every one of Boas's fourteen cases the illness

appeared to commence suddenly at a particular moment when the patient made a violent or unusual effort. This observation would not find favour in the eyes of J. C. Paterson, to whom reference will be made later, and on whose pathological observations Boas largely relies in building up his interesting and apparently complete theory of the pathogenesis of coronary occlusion. Boas thinks that "with physical effort there is a sudden alteration of arterial pressure, cardiac action is increased, rupture of one of the capillaries or sinusoids in the arterial wall may occur, or a softened atheromatous plaque may rupture into the arterial lumen. If the hæmorrhage is large there may be almost immediate occlusion of a coronary artery; if the hæmorrhage is small or slow, or if it is followed by a gradually growing mural thrombus the occlusion may develop slowly or remain incomplete". Boas goes on to remark that when symptoms of coronary disease are induced by physical strain, even when the patient has had no preceding symptoms, there have most likely been antecedent anatomical lesions of the coronary arteries.

J. C. Paterson, who has already been mentioned, has discussed the work of Masters, Dack and Jaffe.² He refers to their conclusion and states that it implies that coronary thrombi are initiated and progress to the point of occlusion in a short space of time. Such an inference, he holds, has no pathological basis. He states that there is evidence to prove that hours or even days elapse between the time of the inception of the thrombus and the moment when occlusion, with its resulting cardiac pain, occurs. To demonstrate this, he adds, one has only to study the structure of the occluding thrombus in a person who, in apparently good health, collapses and dies with the onset of cardiac pain and before infarction has had time to take place. "If a serial section is made through the entire length of the thrombus, some levels will show the process to be many hours or days old." His general conclusions are interesting. On the one hand he states that the activities of a patient immediately preceding the onset of an attack of coronary thrombosis have no relation to the ætiology of the precipitation of a thrombus, but are purely coincidental. On the other hand he adds that the pathological appearances in a series of fatal cases of coronary thrombosis suggest strongly that excessive exercise and emotional stress are intimately concerned in the mechanism of coronary thrombosis. A full account of Paterson's pathological investigations into this whole question was published in 1938³ and should be read by students of this subject. From his observations, which were made *inter alia* on serial sections, he concluded that there were two varieties of hæmorrhage in the *tunica intima* of the coronary arteries, one that occurred with and the other that occurred without thrombosis of the adjacent coronary lumen, and that these were identical in structure and in origin. He points out that if this identity is granted, certain conclusions may be drawn. Intimal hæmorrhage, he states, occurs at the site of thrombosis either from coincidence or as a result or as a cause of the occlusion. His argument is as follows. The factor of coincidence is improbable, as intimal hæmorrhage of some degree has been observed by him at the site of thrombosis in thirty-two out of thirty-seven con-

¹ *The Journal of the American Medical Association*, May 13, 1939.

² *The Journal of the American Medical Association*, March 11, 1939.

³ *Archives of Pathology*, April, 1938.

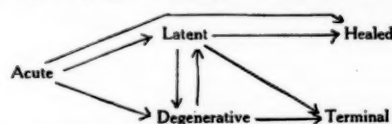
secutive cases. Because discrete intimal hæmorrhages have been found so often in coronary arteries with patent lumina, hæmorrhage cannot be regarded as a secondary intimal change resulting from the presence of an occluding mass in the lumen. By a process of elimination, therefore, the conclusion is reached that intimal hæmorrhage, together with other lesions which appear to result from capillary rupture, is intimately concerned with the aetiology of most coronary thrombi. "Capillary rupture may initiate thrombosis of a coronary artery by diffusion of the blood from an intimal hæmorrhage into the lumen, by necrosis or erosion of the intima from damage to its capillary circulation or by retrograde capillary thrombosis." In regard to Paterson's reference to the implication in the work of Masters, Dack and Jaffe that coronary thrombi are initiated and progress to the point of occlusion in a short space of time, it must be agreed that the implication is there. It is only an implication, however, and not a stated conclusion. The important point about Masters, Dack and Jaffe's observation was that the percentages of cases associated with different forms of rest and activity corresponded closely to the portions of the day spent by most people in rest or activity. Paterson's contention that coronary occlusion is not necessarily a condition that develops quickly is not incompatible with this observation. Paterson wishes us to believe that some of the occlusions that become complete while the patient is asleep or at rest have been initiated while he was active. If Masters, Dack and Jaffe agreed that this might be true, Paterson could not object if they pointed out that in these circumstances it was reasonable to assume that some occlusions becoming complete while the patient was active might have been initiated while he was at rest. It would be interesting to see how Paterson would answer this contention. But as a matter of fact, Masters, Dack and Jaffe have a more weighty argument to advance in defence of their thesis. They point out that it is well known that an increase in arterial pressure is not transmitted to the peripheral capillaries; there is also no proof that an increase in aortic pressure is transmitted to the capillaries arising from the lumen or adventitia of the coronary arteries. They also refer to the failure of Winternitz and his co-workers to produce rupture of intimal capillaries when they injected the coronary vessels of human hearts at a pressure of 500 to 1,000 millimetres of mercury, pressures far beyond any attained during life. They finally mention observations by Horn and Finkelstein, which were in the press when they wrote, in a large series of cases of coronary occlusion; these observations showed that intimal hæmorrhage due to capillary rupture was not more frequent in cases characterized by preceding hypertension than in those in which hypertension was not present.

From the investigations that have been discussed it will be seen that the subject is one of some difficulty. No dogmatic conclusion can be stated, but it must be admitted that the weight of evidence is heavily in favour of the views of Masters, Dack and Jaffe. Their case is so strong that until convincing and irrefutable evidence is found to the contrary it should be accepted as a working rule that effort has no part whatever in the causation of coronary thrombosis.

Current Comment.

ACUTE NEPHRITIS.

THE subject of nephritis is a confused and perplexing one in the minds of many practitioners. The relationship between the various stages of the disease, the bewildering multiplicity of names given to these stages by various writers and the uncertain nature and prognosis of the initial acute attack are among the factors contributing to this confusion. From time to time some worker makes a significant effort to order and to simplify our conception of this disease. The latest of these has come from W. W. Payne and R. S. Illingworth,¹ of the Hospital for Sick Children, London. Two other very valuable contributions to which we would direct attention are those of T. Addis^{2,3} in 1925 and 1931, and of A. W. Snoke⁴ in 1937. Addis devised a method of examining the urine of patients in which he used the centrifuged deposit from a concentrated 12-hour specimen, and estimated the amount of albumin and the number of cells and casts passed in that time. He was able to detect and to follow latent and persistent activity of the disease process in the kidneys of patients who had apparently recovered from an acute attack. He produced the following simplified classification of glomerulo-nephritis.



The acute stage shows the picture so frequently seen of hæmaturia, slight œdema, rise in blood pressure and blood urea, decrease in urinary output, and symptoms like vomiting, lassitude *et cetera*. After several weeks the patient, most often a child, usually appears to recover, and in some cases does. In a considerable number, Addis has shown, the process passes to the stage of latent activity, in which the patient appears to be quite well, but in which persistent slight urinary abnormality is found by Addis's careful method. This stage of latent activity may last many years or only a few weeks, and the outcome may be healing or transition to the degenerative or terminal stages. The degenerative stage is characterized by massive œdema, gross albuminuria, very slight hæmaturia, and little impairment or urea excretion or rise in blood pressure—the hydræmic, nephrotic or parenchymatous nephritis of some writers. The terminal stage presents the well-known picture of chronic nephritis, with marked rise in blood pressure, impairment of urea excretion, retinal changes and death. All these stages need not appear in the course of the disease in every patient. The various possible sequels to an attack of acute nephritis can readily be followed from Addis's graph.

One useful thing that Payne and Illingworth have done is to collect all the titles used in the voluminous modern literature on nephritis and to show that they all refer to one or other of the stages shown in the above scheme.

Many practitioners will remember having seen cases of the degenerative or terminal stages of this disease in which the patient gives no history of a preceding initial acute stage. Snoke produces valuable evidence that the attack of acute nephritis may be so mild as to be missed clinically, but yet may go on to these grave later stages. He too uses the careful urinary examination introduced by Addis. De Wesselow, Goadby and Derry⁵ in 1935 examined the urine in 354 cases of acute tonsillitis for three weeks after the onset of the infection, and found three patients suffering from undoubted acute nephritis and other patients with abnormalities of the urine which would otherwise

¹ The Quarterly Journal of Medicine, January, 1940.

² The Journal of the American Medical Association, July, 1925.

³ The Bulletin of the Johns Hopkins Hospital, October, 1931.

⁴ American Journal of Diseases of Children, March, 1937.

⁵ The British Medical Journal, May 25, 1935.

have passed unrecognized. Evidence accumulates to show that patients like these may pass on to the later stages of the disease, and with Snook's evidence explains those cases in which chronic nephritis appears without an antecedent history of an initial acute attack.

Perhaps the greatest problem that faces the practitioner is not to appreciate the significance of the degenerative and terminal stages of the disease, for the prognosis in these stages is uniformly bad, but to know which of his patients with acute nephritis will recover and in which the condition will pass to the stages of persistent activity. This brings us to Payne and Illingworth's main theme. It has been the habit of many writers in journals and textbooks to make a distinction between two alleged types of acute hæmorrhagic nephritis, the so-called focal and diffuse types. A. J. Collins referred to this distinction in an article in this journal on March 2, 1940. The acute focal nephritis is supposed to occur at the height of some primary infection like acute tonsillitis, and to be characterized by gross hæmaturia, but absence of general symptoms, of œdema, of rise in blood pressure, of oliguria and impairment of nitrogen excretion, and to carry with it a uniformly good prognosis. The acute diffuse type of the disease, however, is supposed to occur a period of some days or even several weeks after the acute primary infection. The patient exhibits hæmaturia, oliguria, œdema (slight or marked), constitutional symptoms and rise in blood pressure and blood urea. The likelihood that these patients may pass on to the more chronic stages of the disease is said to be much greater. Payne and Illingworth have reviewed and followed up a large series of patients with acute nephritis treated in the Hospital for Sick Children in recent years. They reach a conclusion that must have suggested itself, though perhaps vaguely, to any thoughtful worker who has treated many children with acute nephritis. Their conclusion is that acute focal nephritis cannot be recognized as a clinical entity, and that there is one, and only one, type of acute glomerulonephritis. The characteristics that are supposed to distinguish the focal from the diffuse form of the disease are in fact distributed among the cases without apparent relationship to one another. Thus patients with œdema may or may not have oliguria, hypertension and nitrogen retention, and so with each of these characteristics. "The presence or absence of œdema is a useless criterion for the distinction of the two types . . . other criteria . . . were similarly useless." Nor was the presence of any symptom or group of symptoms, or any grouping of the cases, significant in respect of prognosis. The follow-up revealed that the outlook was equally serious no matter which characteristics were present during the acute stage. Payne and Illingworth were unable to follow up a sufficient percentage of the hospital's old patients to estimate accurately how many recovered, but of those who did attend the majority were found to be in the stage of latent activity, and several were found to have died already of chronic nephritis. This is a disquieting revelation, but it is consistent with other recent reports. It must impress us with the fact that acute nephritis is a very grave disease. At present we cannot tell in which of our cases healing will occur and which patients will go on to one or other of the chronic stages. No matter how mild the initial attack, its doubtful prognosis must be accepted. Repeated follow-up examinations for years may be considered worth while, for a rising blood pressure or a persistent urinary abnormality (which may be missed unless the accurate method of Addis is used) will indicate that the die has been cast and the lot of ill-health has befallen the patient.

STERNAL MARROW BIOPSY.

THE last few years have seen a steady growth of interest in the study of the bone marrow in diseases characterized by changes in the circulating blood. This interest grew *pari passu* with the conception of the erythron as an organ and of the interrelationship of its widely scattered parts. The discovery of liver therapy in pernicious anemia aroused tremendous interest in diseases

of the hæmopoietic system and in the study of the bone marrow, for pernicious anæmia is one disease in which pronounced marrow changes are present. Marrow biopsy was carried out on animals as early as 1903 and in humans five years later marrow from the tibia was being obtained by trephining. It was found, however, that tibial marrow commences to undergo a fatty metamorphosis when the child reaches the age of about seven years, and is completely inactive by the age of fifteen. From this age onward tibial marrow yields useful information only in diseases, like pernicious anæmia, which cause changes in the fatty marrow. The marrow of the sternum on the other hand remains active as a hæmopoietic agent throughout the whole of life, and its value for purposes of biopsy has been recognized since 1923. At first the marrow was obtained by trephining, but in 1929 Arinkin introduced the method of sternal puncture, using a needle and aspirating a small amount of marrow for examination. Since that time there has been much argument as to whether trephining or needle puncture is the preferable procedure. Recently both methods were discussed in this journal. In the issue of March 23, 1940, T. E. Wilson expressed his strong preference for trephining. While admitting the simplicity and possibility of repeated use of puncture, he claims that these advantages are greatly outweighed by its inaccuracy, for the relative proportion of cells and their relationship to one another cannot be determined by puncture alone. Moreover, sections can be cut of material removed by the trephine to determine the normal anatomical relations of the elements of the blood to the general structure of the marrow. This, of course, is not possible with the material obtained by puncture. K. Kato,¹ who has made one of the most thorough studies yet published of the bone marrow of children, uses sternal puncture, but admits the shortcomings of the method, in that the material obtained is always to some extent contaminated with blood, and may not give a representative marrow picture because the more adherent cells of the reticulum and capillary walls, the lymphoid accumulations around the capillaries, and small islands of abnormal hæmopoiesis may fail to be withdrawn by suction through a needle. P. Vogel and F. A. Bassen,² in a more recent review of the procedure in children, strongly prefer puncture to trephining. They point out that, because of the thin sternal plate of the child, puncture is extremely simple, and trephining may be dangerous. "The advantages of sternal aspiration are numerous. In addition to the ease and safety of the procedure is the fact that it may be repeated as often as one considers necessary. Absence of a resulting scar and of danger of infection are additional advantages. The pain . . . is hardly more than momentary. . . . It may be performed at the bedside, in the office or clinic or at home. . . . The aspirated material may be spread and examined immediately. The condition of the cells is far superior to that seen in sections, where the process of decalcification causes artifacts and shrinkage of the cells, making them difficult if not impossible to recognise." J. A. McLean, in this journal of October 26, 1940, describes useful results obtained by puncture, preferring this method because of its simplicity.

These workers have each used one method, for one reason or another regarding it as superior for their purposes. An interesting comparison of the two methods was supplied by Dameshek, Henstell and Valentine in 1937.³ In twenty cases, material they obtained by both methods was examined. Puncture of the sternum was done first; a small amount of material was aspirated and used for the preparation of smears. Immediately afterwards a trephine was used to remove a small plug of bone. This was used for the preparation of sections. A small amount of the marrow laid bare by the removal of the plug was collected in a curette, and smears were prepared from it. As a result of this comparison the authors were overwhelmingly in favour of trephining. They obtained the definite impression that in the one case (puncture) they were dealing with blood containing a few marrow cells, whereas

¹ *American Journal of Diseases of Children*, August, 1937.

² *Ibidem*, February, 1939.

³ *Annals of Internal Medicine*, November, 1937.

in the other (trephining) they dealt with marrow interspersed with some blood cells, and they concluded: "When the procedure of bone marrow biopsy is contemplated, we feel it should be done in as careful a manner as possible, since, even with the best technique, interpretation may be difficult."

The matter seems to be by no means settled, and further comparative studies such as the last one described would be of great value. They should include normal patients as well as those suffering from diseases of the hæmopoietic system, for our conception of the normal findings from each procedure is as yet by no means fixed. It may well be found that each procedure has a place of its own as a diagnostic aid. In the meantime any carefully conducted study by either method must be welcomed as adding to the sum of our knowledge.

Diseases of the erythron in children offer to the student of the bone marrow a field with certain special features. In the first place, the diseases of the hæmopoietic system of children are at present more confusing than those of the adult. Leonard Parsons, one of England's ablest pædiatricians, has stressed the varied and inconstant picture displayed by diseases of the child's erythron. Though our classification of anæmia in adults is not completely satisfactory, it is usually possible to place the anæmia from which an adult is suffering into a definite disease group. Not so, Parsons pointed out, with children. All too frequently it is many weeks before a disorder of the erythron of a child can be labelled with certainty, and some cases evade classification to the end, for the immature erythron responds to stimuli in ways more varied than in the adult. In the second place, the anatomy of the sternum in the child differs materially from that in the adult, necessitating variation of the technique of sternal biopsy. We therefore welcome a survey by M. Diwany¹ of sternal puncture in children. He wisely approached the problem by making a radiological and naked-eye study of the child's sternum at various ages to determine the developmental stages of the ossification centres, the site of the pools of bone marrow and the depth to which the needle need be inserted. Ossification centres first appear in the sixth month of intrauterine life. By the time the infant is eight months of age the centre for the manubrium and the first sternebra have fused, providing a considerable localized marrow mass. The centre for each sternebra is opposite the intercostal space. Opposite the costal cartilages are cartilaginous septa separating the ossification centres. Sternal puncture should therefore always be made opposite an interspace. These septa disappear as adult life is reached and puncture can be made anywhere along the sternum. In the infant of but a few months the centre for the manubrium is largest and should be used. Care, however, must be taken not to perforate the posterior lamina of the sternum and damage the large vessels of the superior mediastinum. In older children the centre for the second sternebra should be used. It lies opposite the second intercostal space, just below the prominence of the sterno-manubrial ridge. The anterior lamina of the sternum is cartilaginous in young children, and care and skill are necessary to tell when the marrow is entered. When this is done 0.1 to 0.2 cubic centimetre of marrow is withdrawn by strong suction with a ten cubic centimetre syringe, a procedure causing distinct pain. It is foolish to try to withdraw more marrow than this, for admixture with blood is then sure to occur. The needle used is a short lumbar puncture needle, complete with stylette, and fitted with an adjustable shield to prevent penetration to too great a depth. The depth recommended is 0.5 to 0.8 centimetre, depending on age and obesity.

Diwany investigated the marrow of normal children and of several children with ankylostoma anæmia, bilharziasis and cretinism. We are not concerned to discuss his results except simply to point out that he found in ankylostoma anæmia an erythro-normoblastic reaction, in bilharziasis an eosinophilic reaction and in cretinism marrow hypoplasia. What we would stress is that he has carefully described, with excellent illustrations, a study in this

special field. More of these are needed, and for the time being we feel that attention should be directed especially to a comparison of the findings by the use of trephine and needle in the same patients, including both those whose bone marrow is expected to be normal and those in whom it is known to be diseased.

ACUTE HÆMATOGENOUS OSTEOMYELITIS.

An important study on acute hæmatogenous osteomyelitis has been published by E. C. B. Butler.² It is based on records of 500 cases occurring in patients admitted to the London Hospital during the years 1919-1937. The first fact brought to the notice of the reader is that acute osteomyelitis is a diminishing disease in the East End of London. Between the years 1919 and 1928 the patients admitted to the hospital with this condition numbered 344; but from 1929 to 1937 the number was 156. The only cause found for this diminution is the better health and home conditions that now prevail; this must be regarded as satisfactory from every point of view. There was a history of injury in 43% of cases; a primary focus was noted in only 93 cases. Butler shows that the mortality is due in the majority of cases to staphylococcal septicæmia. He and Valentine have made the reasonable suggestion that the primary focus rather than the infected bone may sometimes be held responsible for the maintenance of bacteriæmia. The case histories that he gives in support of this view are interesting, but unfortunately rather shorn of detail that might have been entirely convincing. It is interesting to note that the death rate remained practically constant in each consecutive hundred cases, despite the decreased incidence and the conservative treatment adopted during recent years. More important perhaps is the observation that the immediate prognosis was but little affected by the various surgical procedures that were adopted. Of the five hundred patients, 469 were submitted to operation on admission to hospital or shortly afterwards. Of 117 patients whose periosteal abscesses were drained, 24 died, a mortality rate of 21%; of 280 in whom the medullary cavity of the bone was drained, 60 died, a mortality rate of 22%; of 41 in whom the bone was drilled, eight died, a mortality rate of 20%. Butler is very fair, because he questions the inclusion of the last percentage, 20, on account of the small number of cases in which drainage was performed. There is not sufficient space to follow Butler's discussion on blood culture; but we would emphasize his statement that a persistent or increasing bacteriæmia, indicating that organisms are being thrown off into the blood stream from some infected thrombus, is of grave significance. The site of this thrombus may be the original septic focus, the infected bone, or some other focus elsewhere in the body. Most surgeons will agree with Butler that in severe cases, when the bacteriæmia, as judged by "quantitative blood-culture", is high, excision of the primary focus is justifiable to eliminate a possible source of infection. If the focus responsible for the continuance of bacteriæmia is a thrombus not situated in the primary lesion, it would surely be equally justifiable, if possible, to excise it. Of the patients who died, 34% died in the first week and over 66% in the first fourteen days. "The patients who died in the first week did so from an acute bacteriæmia against which surgery was of no avail." Butler adds that the mortality rate of osteomyelitis will continue to be high until methods are found that will conquer infection of the blood stream by the staphylococcus. The series of cases reported by him occurred in the pre-sulphanilamide era; but he states that though individual triumphs from the use of drugs of the sulphanilamide group have been reported, no large series has been published. He has used sulphanilamide, "Uleron" and "M & B 693", but without appreciable effect. He thinks that antistaphylococcal serum with antileucocidin antibody may be useful, but for surgical treatment pins his faith chiefly to rest and the relief of tension.

¹ Archives of Disease in Childhood, September, 1940.

² The British Journal of Surgery, October, 1940.

Abstracts from Medical Literature.

PÆDIATRICS.

Simultaneous Immunization against Whooping Cough and Diphtheria.

HARRY SCHÜTZE (*The Lancet*, August 17, 1940) has carried out experiments on guinea-pigs and rabbits in regard to simultaneous immunization against diphtheria and whooping cough. As the efficiency of whooping cough vaccine becomes more generally accepted and the practice of active immunization against diphtheria more widely adopted, it would be an obvious convenience to combine prophylactic measures against the two diseases and to administer both immunizing agents simultaneously (Bordet, 1936; Ledingham, 1939). Before this can be advocated with confidence it is necessary to be assured that the two prophylactics do not interfere with each other in their antigenic effects. The author's experiments demonstrate the compatibility of diphtheria toxoid and pertussis vaccine. In neither case does the antigen potency of the one suffer by the inclusion of the other in the inoculum. It may therefore be concluded that it is both convenient and effective to carry out simultaneous immunization against diphtheria and whooping cough in children.

Lingual Application of "Eumydrin" in Congenital Pyloric Stenosis.

ARVID WALLGREN (*Archives of Disease in Childhood*, June, 1940) draws attention to and recommends a method of treatment of congenital pyloric stenosis by the lingual application of a concentrated alcoholic solution of "Eumydrin". A growing interest in the conservative treatment, and especially in "Eumydrin" treatment, of this condition seems to have been aroused among British paediatricians by Svensgaard's article four years ago. The treatment has been widely used in Germany and Scandinavia for many years. All those who have employed "Eumydrin" in congenital pyloric stenosis agree that it is usually effective, but there is no agreement as to the requisite dose nor as to the mode of application of the drug. Before "Eumydrin" was introduced, atropine or papaverine was the remedy of choice in the conservative treatment of pyloric stenosis on the Continent and in Scandinavia. These drugs were given by the mouth in aqueous solution and in varying doses, and toxic symptoms were rather frequent. Lindberg drew attention to the fact that alcoholic solutions of atropine kept their strength and were much more durable than aqueous solutions, and recommended their use. He also advised the giving of the alcoholic solution perlingually instead of by mouth. When "Eumydrin" was introduced the author abandoned atropine and applied the less toxic "Eumydrin" in the same way as atropine had been used; a 0.6% alcoholic solution of "Eumydrin" contains approximately 0.1 milligramme of "Eumydrin" in each drop. A drop of this solution placed on the tongue is rapidly absorbed and the treatment and absorption are not interfered with by vomiting. It is usual to begin with one to two drops a day and to increase the dose gradually if necessary until the vomiting becomes

less severe. The earliest sign of toxic effect is a flushing of the face, and if this appears the dose is reduced. It has seldom been necessary to exceed 0.3 to 0.5 milligramme of "Eumydrin" a day. This method has been employed as a routine treatment of pyloric stenosis for the past twelve years, and the mortality rate of the Gothenburg infants suffering from this disease has been 1% during this period. The advantages of this method as compared with the oral treatment by "Eumydrin" in aqueous solution are evident. In the latter mode of application a certain and variable amount of the drug is rejected by the vomiting, and this makes careful dosing impossible. When there is intense vomiting most of the drug is rejected before absorption; when the infant occasionally stops vomiting for a day or two and the same dose of "Eumydrin" is used, most of the drug given is perhaps absorbed. In this way it may happen that sometimes too much "Eumydrin" is absorbed and, although the drug is far less toxic than atropine, it may cause serious intoxication and even death. By lingual application of a concentrated alcoholic solution of "Eumydrin" the dose absorbed is known and is independent of the severity of the vomiting, whilst the solution keeps its strength without obvious deterioration of the drug. It is clear that toxic symptoms can be prevented much more certainly in this way.

Prophylactic Inoculation against Whooping Cough.

I. H. MACLEAN (*Proceedings of the Royal Society of Medicine*, May, 1940) discusses prophylactic inoculation against whooping cough based on experiences at the clinic at Saint Mary's Hospital. Up to 1930 most stock pertussis vaccines were made from old laboratory strains of *Haemophilus pertussis*, rough from cultivation on unsuitable medium. Leslie and Gardner (1931) described S → R variation which takes place when strains of *Haemophilus pertussis* are grown for long periods on laboratory medium. In the author's experience all newly isolated strains have smooth colonies and are fully virulent. These are the Phase I strains of Leslie and Gardner, who traced the degeneration of their newly isolated strains through various phases until they eventually reached Phase IV, the permanently rough state. Pertussis vaccine should be made only from strains which are in Phase I and which are either newly isolated or have been maintained in Phase I by growth on Bordet-Gengou medium. Most of the recent work on the prophylaxis of whooping cough has been done with vaccines made from strains of Phase I. The literature of the last nine years contains records of some twenty thousand children who have been inoculated against pertussis, and the attack rate in most cases was under 5%. The communicability rate is the percentage of exposed children who eventually contract the disease. It shows an approximate average in the inoculated children of 10% compared with a communicability rate in controls from 60% to 90%, according to the severity of the epidemic. It is perhaps significant that the communicability rate in both inoculated and control groups rises steadily with the intimacy of contact and exposure, showing that artificially acquired immunity, like natural immunity, is only relative. Inoculation greatly modifies the course of the disease, and all but a small

percentage of cases in the inoculated group are classified as mild or atypical. When failures of immunization are reported in vaccinated children it should be remembered that there are many spasmodic coughs simulating whooping cough, and that bacteriological control should be exercised in a suspected case. A correct clinical diagnosis of whooping cough is important, but frequently this is lacking. A reliable bacteriological guide to control the diagnosis can be found only in the cough plate method. The author found that the cough plate gave a positive method of diagnosis in approximately 90% of cases during the catarrhal stage and first week of the disease, whilst in the third week not more than 50% were positive. The author also found that the cough plate method revealed that during a year more than half the patients notified as suffering from whooping cough in the western district of London and referred to the clinic were not infected by *Haemophilus pertussis*. In regard to the choice of antigen, a simple suspension of killed Phase I strains is the only antigen which has so far proved of value in recent field experiments. Undenatured bacterial antigen (Krueger, 1933) at first had a very great following, but it has been shown by Lawson experimentally and by Singer-Brooks clinically to have no value as a prophylactic. The antigens in diphtheria toxoid, originally prepared in solution, are now deliberately precipitated by alum to make them more effective. Harrison, Franklin and Bell have reported favourably on the use of alum-precipitated pertussis vaccine. Ledingham (1939) has suggested the combination of pertussis vaccine with alum-precipitated diphtheria toxoid, and the author has found that in this combination the vaccine contained a good antigen and stimulated the production of both agglutinins and productive substances in mice. The optimal dose of pertussis vaccine for prophylaxis has not yet been settled. In America large doses are generally favoured. Sauer started with a dose of 22,000 million bacteria and rapidly increased it to 80,000 million. The author considers that such large doses put too heavy a strain on the process of immunization in the young child and that immunity is delayed. In prophylactic inoculation the primary dose need not be more than the amount necessary to initiate the child's immunizing mechanism and prepare it to respond quickly to a later stimulus, either the actual infection or another dose of vaccine. Effective prophylaxis consists in a primary stimulus followed by a secondary stimulus after an appropriate interval. Pertussis vaccine is a slow immunizer and doses must not be given too close to one another. It is far better to allow an interval of one month before stimulating doses are given. With these points in view the author has for four years used the following scheme of dosage. Dose 1: 4,000 million with an interval of three to seven days. Dose 2: 4,000 million with an interval of three to seven days. Dose 3: 4,000 million with an interval of at least a month. Dose 4: 4,000 million. In a test group of 513 children with 46 known and 45 suspected exposures, not a single case of whooping cough occurred. In the control group of 154 children with 115 exposures, 89 cases of the disease developed. An additional dose of 4,000 million organisms should be given subsequent to the immuniza-

tion course when the child is known to have been exposed to the infection or starts school life. The earliest age at which immunization can be successfully attempted is between six and twelve months. Children of this age may safely be given the full scale of dosage, and from this period until seven or eight years of age they respond well and are easily immunized. New-born children have been immunized by vaccines, but it should not be lightly undertaken. In the author's experience the best method of prevention in very young children is to isolate them from the infected members of the household by placing them under a muslin covering, and if exposure is known to have taken place, to attempt passive immunization by the use of convalescent serum. Immunity in whooping cough, both naturally and artificially acquired, is generally considered to be lifelong; but there are cases of apparently genuine second attacks.

ORTHOPÆDIC SURGERY.

Localized Volkmann's Contracture.

JOHN BRUCE (*The Journal of Bone and Joint Surgery*, July, 1940) describes a case of Volkmann's contracture affecting the middle finger of one hand. The typical condition is generally a complication of severe injury in the region of the elbow joint. The injury in this particular patient was a contusion of the forearm, caused by a blow from a tennis ball. Swelling, bruising and discoloration appeared early. Three weeks later the middle finger was flexed at the metacarpophalangeal joint, and active extension was impossible. The deformity was due to contracture of the *flexor sublimis digitorum* fibres to the middle finger. At operation the tendon was lengthened by the sliding method, and a plaster cast with the finger in extension was applied for six weeks. Subsequently massage and movements were employed, with complete restoration of function.

Internal Fixation of Fractured Clavicle.

GORDON MURRAY (*The Journal of Bone and Joint Surgery*, July, 1940) describes a method of fixing fractured clavicles which he has applied in twenty-nine cases. Most of the methods usually practised will hold the fragments in satisfactory position, but the splints or supports have to be tightly applied, with resulting pain and discomfort. Practically all fractured clavicles unite, and the functional result is good. The cosmetic and anatomical results, however, are frequently disappointing, especially in women. Under general anaesthesia the author first obtains perfect reduction. A quarter-inch incision is then made over the clavicle, one inch from the medial end. A quarter-inch hole is drilled into the centre of the bone, and along this a Kirschner wire is directed so as to bridge the fracture site. The wire is cut short and the medial end is allowed to disappear under the skin of the incision. This permits easy removal if required. Where open reduction is necessary, this is performed through a small incision over the fracture. The wire is then directed along the medullary canal of the lateral fragment until it pierces the skin at the shoulder. Then with use of the drill from this end the

wire is directed across the fracture to the medial fragment. Care must be taken in directing the wire to ensure that it does not pass posteriorly, with the possibility of injury to the apex of the pleura, the subclavian vessels or the brachial plexus. Full range of shoulder movement is obtained once the patient recovers from anaesthesia. No fixation, except a sling, is required. In the twenty-nine cases there has been no complication or infection.

Mechanical Derangements of the Knee and Shoulder.

MELVIN S. HENDERSON (*The American Journal of Surgery*, June, 1940) discusses some common conditions of the knee and shoulder joints. The various types of lesion of the knee cartilages are described, with their method of production. Operation after the first dislocation is not advised except when reduction by manipulation is impossible. For removal of the cartilage a vertical incision is employed with the knee flexed to a right angle. In a series of 343 operations no relief was obtained in 7.4%. This was thought to be due to a concomitant injury to the cruciate ligaments. Whereas cartilage injuries usually affect men, recurrent dislocation of the patella more often affects young women. A family history of the occurrence may sometimes be obtained. The diagnosis is not always easy. The operation recommended is removal of the insertion of the *ligamentum patellæ* with a portion of the tibial tuberosity, and its transplantation onto the medial surface of the upper end of the tibia. For about a year there may be some difficulty in flexing the knee, owing to alteration in the relation between the articular surfaces of the femur and patella. For habitual or recurrent dislocation of the shoulder joint an operation of tenosuspension has given the best results. A length of *peroneus longus* tendon is used and an extraarticular suspension from the acromion process to the greater tuberosity of the humerus is performed. Of 29 patients so treated, 26 had no further trouble.

Treatment of Dupuytren's Contracture.

HENRY W. MEYERDING (*The American Journal of Surgery*, July, 1940) reviews the treatment of Dupuytren's contracture since the condition was first described by Dupuytren in 1832. Operative treatment became the method of choice early. There is a great difference in the rate of progress of the disease, and deformity may be arrested and may cease to increase for many years. In some cases there is no tenderness or redness associated with the contracture; in others, pain, swelling and local redness are present. The region first involved is the palmar aspect of the metacarpophalangeal joint of the ring finger. Repeated trauma to this region is common, and when it is associated with some toxic irritant that acts systemically, the author believes that irritation of the palmar fascia and fascial hypertrophy may be caused. In some cases of slight deformity subcutaneous fasciotomy may produce relief if great care is taken to avoid injury of blood vessels, nerves and tendons. The most successful treatment consists in removal of the contracted palmar fascia and the application of proper post-operative measures. Incisions are made along the fifth metacarpal bone and transversely along the *linea mensalis*. An

antero-lateral incision is made for dissecting fascia in the fingers. The author first exposes the upper end of the fascia, clamps and divides it. It is then drawn away from the palm and the fasciculi are divided as they pass out. The whole of the contracted fascia is freed and, should it continue into the fingers, separate incisions and dissections are made. Care must be used in freeing blood vessels and nerves from the fascia. A bloodless field is maintained by a sphygmomanometer cuff, the cuff being released occasionally that the bleeding vessels may be tied. The wound must be dry before it is closed. No drainage is used. A well-padded posterior aluminium splint is applied to hold the involved fingers in extension. Dressings are changed at the end of a week. The author allows the wound to heal before beginning movement, the splint being applied at night until free movement is obtained.

Acromio-Clavicular Dislocation.

A. A. APPELL (*The Canadian Medical Association Journal*, July, 1940) states that dislocations of the acromio-clavicular joint are usually treated by adhesive strapping for a number of weeks. At times the disability is underestimated and patients are dismissed with a few words of reassurance. The condition is usually caused by street accidents and on the athletic field. When a man earns his livelihood by heavy manual labour, the resulting instability of the affected shoulder greatly interferes with his earning capacity. The author, describing the anatomy of the joint, states that the thin acromio-clavicular ligament is weak. The coraco-clavicular ligament, which passes from the coracoid process to the under-surface of the outer end of the clavicle, is much stronger. In the cadaver, section of the acromio-clavicular ligament produces little effect on the stability of the joint. If, however, the conoid and trapezoid ligaments are cut, the outer end of the clavicle readily dislocates upwards. In a patient with such an injury the deformity is readily palpable, there is instability of the joint, and difficulty in abducting the arm beyond 90°. There is a constant nagging pain in the region. The author states that recent acromio-clavicular dislocations should be treated for two months with strapping. If by that time there is no improvement, it is obvious that the coraco-clavicular ligaments are torn and surgical repair is necessary. The operation he describes consists of exposing the joint and the coracoid process by dividing the clavicular head of the deltoid. Two drill holes are made in the outer end of the clavicle and one through the acromion. A strip of *fascia lata*, half an inch wide, is threaded through one acromion drill hole, passed under the coracoid process, tied and oversewn. This constitutes the new coraco-acromial ligament. A second *fascia lata* strip connects the remaining two drill holes, forming an acromio-clavicular ligament. The detached deltoid is sutured to the clavicle and the operation is completed. A drain is inserted subcutaneously for twenty-four hours. After-treatment consists of maintaining the arm at right angles with pillows for three or four days, followed by the wearing of a plaster shoulder spica with the arm abducted for five or six weeks. Active and passive movements and massage are then used to hasten the return of normal function.

Special Articles on Psychiatry in General Practice.

(Contributed by request.)

XXVIII. TESTAMENTARY CAPACITY.

THE general practitioner needs a sound knowledge of the law relating to testamentary capacity, as he is frequently called upon to witness a patient's last will. It is assumed, when a doctor thus witnesses a patient's will, that he tested the patient in such a way as to be able to certify that the patient at the time was of sound disposing mind. It often happens, when a will is made in these circumstances, that there also exists an emotional atmosphere which tends to upset the judgement of both the patient and the doctor, and greater care is needed to ascertain the patient's capacity than when a will is made in calmer circumstances.

The law concedes the right to every person to dispose of his property as he thinks fit, and allows him very great freedom in this regard; but it also insists that when such a disposition is made the testator is possessed of those intellectual and moral qualities which are commonly enjoyed by mankind.

The principles by which the courts decide whether a person is possessed of testamentary capacity at the time of making a will are as follows: (i) that the person understands the nature of the business that he is transacting (that is, making a will), and also has sufficient memory and understanding to recollect the nature and approximate extent of the estate that he is about to bequeath; (ii) that he remembers each and all of the persons who may have some claim on his bounty, whether by ties of blood or of affection, and that he understands the relationship of the beneficiaries to himself and their respective claims upon him; (iii) that he has sufficient mental strength to keep the above two first principles in his mind long enough to form a rational judgement about them. But, as it was so well put in *The British Medical Journal* of April 13, 1935:

He need not be, in the ordinary sense of the word, completely sane, and he certainly need not have an accurately balanced mind. He may be feeble with age or racked with pain, and need not be completely sober. He may give way to caprice, or malice, as he chooses; he may leave all his property to a mistress or a hospital and nothing at all to his wife and children. The law merely requires that he shall be of age and be acting of his own volition. This volition must be that of a mind of natural capacity, not unduly impaired by old age, enfeebled by illness, or tainted by morbid influence.

The following are the main factors which may so affect a testator's mind as to make his will invalid: mental disease, mental deficiency, physical disease, senility and drunkenness.

Mental Disease.

The mere presence of mental disease does not of itself invalidate a will, because the patient's capacity in this regard is determined at the actual time of making the will. The will is invalid if the derangement of the mind is such as to make him incapable of understanding the nature and effects of his act. However, he need not understand the legal phraseology in which the will is expressed.

Delusions.

Although the presence of delusions always indicates a widespread and severe disorder of the mind, and while from a psychiatric point of view all conclusions of such a mind may with reasonable suspicion be thought to have their foundations in irrationality, nevertheless the law demands that to invalidate a will, a delusion, if it can be proved to have existed, must have affected the testator while he was actually making the will. It has to be proved to the satisfaction of the court that the delusion influenced his mind in the disposing of his property in such a way that, if the mind had been sound, he would have made different provisions. If the testator, at the time of making a will, has any delusions regarding his actual property or concerning any of those persons who have a natural claim on his bounty, or if the will is actually shown to have been made as the result of a delusion, the court will look with suspicion upon such a will, even if such delusions may not actually appear to have influenced the disposition of his property.

General Considerations.

The doctor should read the will to the patient himself and make sure that the patient understands each separate bequest, and inquire as to the contents of any previous will and the reasons for any marked change of disposition, and note these down as he goes along. He should be satisfied that the will is a sensible one, and, if this is so, the court is generally reluctant to set it aside. He should question the patient as to the nature and extent of his property and about those who have a claim on his bounty, and write these down in the form of answer and question at the time of examination. He should be satisfied that the patient is not unduly under the influence of alcohol or other sedatives.

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British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on September 10, 1940, at Saint Vincent's Hospital. The meeting took the form of a number of clinical demonstrations by members of the honorary staff of the hospital. Part of this report appeared in the issue of December 28, 1940.

Diversion of the Urinary Stream in Tuberculosis.

DR. HENRY MORTENSEN first showed a male patient, aged forty-eight years, who had been treated since June, 1938, for genito-urinary tuberculosis. He had undergone the following operations: left nephrectomy (August, 1938), left orchidectomy (July, 1939), left ureterostomy (January, 1940), and right nephrostomy (June, 1940). The patient's condition prior to his last operation was pitiful owing to his constant desire to micturate. This precluded sleep, and he was rapidly losing condition. Cystoscopic examination was impossible even under anaesthesia, owing to the smallness of his bladder, and no definite proof was available as to whether his right kidney was free from tuberculous infection. However, an excretion pyelogram revealed a progressive hydronephrotic change, and this, associated with a rise in the blood urea level from 29 milligrammes per 100 cubic centimetres in July, 1939, to 75 milligrammes per 100 cubic centimetres in May, 1940, indicated the necessity for some operative procedure.

Right nephrostomy was performed, and the urine drained from this was found to be free from tubercle bacilli; it might be possible at some later date, when his condition became stabilized, to transplant his ureter to the colon. His improvement had been remarkable. He had gained in weight and strength and was able to proceed without inconvenience with his usual occupation.

Dr. Mortensen's next patient was a male, aged twenty-four years, who had been under observation since November, 1937, complaining of frequency of micturition, scalding and haematuria; shortly after that date tubercle bacilli were found in his urine. A cystoscopic examination revealed a bladder capacity of 40 cubic centimetres; catheterization of the ureters was impossible. An excretion pyelographic examination revealed no excretion of dye from the left side, and some dilatation of the pelvis, calyces and ureter on the right side. The patient was regarded as suffering from bilateral urinary tuberculosis, and no operative procedure was carried out.

In June, 1938, he exhibited tuberculosis of the seminal vesicles and bilateral epididymitis; a course of tuberculin injections was commenced. He was seen on odd occasions over the next two years, and clinically presented no change in his signs and symptoms. An excretion pyelographic examination in July, 1940, revealed a gross hydronephrosis. On the grounds of impending kidney failure due to this dilatation, and from the urgency of his symptoms, a diversion of the urinary stream was decided upon, and through an iliac incision a cutaneous ureterostomy was performed. The symptomatic relief was complete. Examination of a section from the ureter revealed no evidence of tuberculosis. In the urine from that side a fair number of pus cells were found; *Bacillus coli communis* was grown in cultures, but no tubercle bacilli were seen or obtained on attempts at culture.

Chyluria.

Dr. Mortensen then showed a female patient, aged sixty-five years, who had been in good health until December, 1939, when she first noticed that her urine was milky and cloudy, with white jelly-like clots occasionally streaked with blood. Some frequency of micturition was present, and she had to pass urine during the night; she had no pain or colic, but had lost one stone in weight in six or eight months. Her general health was good. She had undergone hysterectomy and appendectomy at the Women's Hospital, and had had typhoid fever forty years earlier. She was born in Brisbane and had lived there till the age of forty-six years.

On June 20, 1940, a cystoscopic examination revealed normal bladder mucosa; the base of the bladder was covered with white curd. A bladder specimen of urine was milky and contained a large amount of fat, a fair number of red blood cells, and a number of pus cells; it yielded no growth on a nutrient medium. Specimens of urine from both ureters contained red blood cells and no pus cells, and were sterile. No fat was found in either of the ureteric specimens. An excretion pyelographic examination revealed no abnormality and no sign of any connexion between the lesion and the lymphatic system. Examination of subsequent specimens taken from either ureter revealed fat in each specimen. On many occasions no evidence of *Filaria* was found in the blood or urine.

Dr. Mortensen pointed out that in 80% of filarial cases the embryo *Filaria* was found in the peripheral blood and in 50% in the urine. As the patient had lived in Brisbane, the possibility was that her chyluria had a filarial basis, in spite of the repeatedly negative results of examination of the urine and blood.

Subcutaneous Injection of Dye and Pyelography.

Dr. Mortensen showed films from a case in which pyelography had been carried out after subcutaneous injection of a dye. Twenty cubic centimetres of "Uroselectan B" had been diluted with 80 cubic centimetres of sterile normal saline solution, and equal quantities had been injected in either scapular region. Some dye was seen in ten minutes in the first film exposed, and excellent filling was shown in forty-five minutes. Dr. Mortensen said that the method was of great value for children or for thin women with small veins.

Pulmonary Collapse.

Dr. W. NEWING showed three patients to illustrate the phenomenon of pulmonary collapse. The first was a member of the Australian Imperial Force, aged thirty-five years, who had been in camp for three months; eight weeks prior to the meeting, during an attack of bronchitis associated with violent coughing, it was noticed that some gross abnormality was present. An X-ray examination revealed massive collapse of the right lung and the patient was discharged from the Australian Imperial Force. He recovered from the bronchitis, returned home to his farm and had been doing light work, feeling quite well. At the time of the meeting massive collapse was still present, and no reexpansion had occurred. The right side was immobile, dull to percussion, with little air entry. The heart and trachea were displaced far over to the affected side (right).

Another member of the Australian Imperial Force, aged twenty-one years, had collapse of the upper lobe of the right lung. This young man had been in hospital twelve months previously with a similar collapse, associated with cough and sputum. He had then been suspected of being tuberculous; but exhaustive tests had all given negative results, and the lobe reexpanded, with disappearance of all symptoms in two months. He subsequently joined the Australian Imperial Force, passing the X-ray examination as fit. During an attack of bronchitis in camp the condition recurred and he was discharged as unfit. At the time of the meeting the lobe had reexpanded and he was at work, free from symptoms.

The third patient shown by Dr. Newing had collapse of the lower lobe of the right lung following operation under general anaesthesia—a type not uncommonly seen. The lung had reexpanded within a fortnight.

Dr. Newing said that the distinguishing features of pulmonary collapse were pronounced displacement of viscera to the affected side and the sharply demarcated edge shown in lateral films in lobar cases. The physical signs varied greatly. The area was usually dull to percussion, with little or no breath sounds. On the other hand, cavernous breathing and pectoriloquy, resembling cavitation, might be heard. The theories of causation were not satisfactory. A large plug of mucus was probably responsible in those cases in which rapid reexpansion occurred; but that would not explain the first and second cases.

(To be continued.)

Naval, Military and Air Force.**APPOINTMENTS.**

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Numbers 248 and 258, of December 12 and December 19, 1940.

CITIZEN NAVAL FORCES OF THE COMMONWEALTH.**Royal Australian Naval Reserve.**

Appointments.—John Russell is appointed Surgeon Lieutenant, dated 22nd November, 1940.

AUSTRALIAN IMPERIAL FORCE.**Australian Army Medical Corps.**

To be Colonel.—Lieutenant-Colonel C. E. Wassell, D.S.O., E.D., and to command an Australian General Hospital, 17th October, 1940.

To be Captains.—Captains G. R. Jones, A. C. R. Sharp, G. W. Verco and R. F. K. West, 1st November, 1940.

The regimental seniority of Captain J. Kingsley is next after Captain J. F. Akeroyd.

AUSTRALIAN MILITARY FORCES.**NORTHERN COMMAND.****First Military District.****Australian Army Medical Corps.**

To be Major (temporarily).—Captain N. J. McDermott, 2nd November, 1940.

The following officers are appointed from the Reserve of Officers (A.A.M.C.): Major H. M. Saxby, 16th September, 1940; Honorary Major N. W. Markwell and to be Major (provisionally), with regimental seniority next after Major H. M. Saxby, 16th September, 1940, Captain G. M. S. May, with regimental seniority next after Captain N. Geaney, 4th August, 1940.

The following officers are appointed from the Reserve of Officers (A.A.M.C.), and to be Captains: Honorary Captains M. J. Hishon, with regimental seniority next after Captain C. C. Wark, 24th June, 1940, S. F. M. Yeates, with regimental seniority next after Captain A. Fryberg, 13th July, 1940, P. McL. Davidson, with regimental seniority next after Captain S. F. M. Yeates, 14th July, 1940, and N. Geaney, with regimental seniority next after Captain T. L. Gorman, 30th July, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains.—Herbert John Garnham Hines and Edward William Gibson Parker, 19th October, 1940.

To be Honorary Captains.—Cyril Vincent James, 30th October, 1940, and Neil Tolmie McRae Yeates, Arthur Francis Kelly and Glenloth Victor Hickey, 8th November, 1940.

EASTERN COMMAND.**Second Military District.****Australian Army Medical Corps.**

To be Captains (provisionally).—Frederick Ninian Lynch, 2nd October, 1940; Samuel Bolam Hatfield, 8th October, 1940; and William Kenneth Manning, 9th October, 1940.

The resignation of Captain J. S. Robertson of his commission is accepted, 29th July, 1940.

To be Captains (provisionally).—George Bruce Dalrymple Hall, John Frederick Clair Camplin Cobley, Tristram Essex Holcombe, Nathan John Clements, and Thomas Moore Clouston, 26th October, 1940; Joseph Harry Coles, 30th October, 1940, and Edmund Francis Fletcher, 6th November, 1940.

The provisional appointment of Captain W. McP. Roberts is confirmed.

To be Major (temporarily).—Captain (provisionally) J. I. Robertson, 19th September, 1940.

To be Captains (provisionally).—Kenneth Tamworth Hughes and Edward Seavington Stuckey, 26th October, 1940; Rodney James Hudson, 6th November, 1940; John William Best and Stuart Vance Marshall, 13th November, 1940; Frank Augustus Essery Lawes and Harold Evan Thomas, 15th November, 1940.

Lieutenant C. R. B. Richards is transferred from Royal Australian Artillery (M), Artillery Survey, and to be Captain (provisionally), 2nd September, 1940.

Captain J. R. B. Beaumont is transferred to the Reserve of Officers (A.A.M.C.), 1st November, 1940.

Australian Army Medical Corps Reserve.

To be Captain.—William Siegfried Dawson, 1st October, 1940.

To be Honorary Captains.—Geoffrey Langford Howe, 28th August, 1940; Lachlan Alexander Harlock, 26th September, 1940; Roy Bowman Holliday, 28th September, 1940; Vincent Harcourt Vernon and Gerard Hindley Herbert Gall, 2nd October, 1940; Alan Frederick Smith, 4th October, 1940; Robert Delmont Puffett, 8th October, 1940; Herbert John Solomon, 9th October, 1940; and Frank Moulton Clifford Jones, 17th October, 1940.

To be Honorary Majors.—William Cotter Burnell Harvey, Gavin Bruce White, and John Alexander McGeorge, 28th September, 1940.

To be Honorary Captains.—Vincent Goldrick, 23rd October, 1940; Francis Patrick Christopher Claffy, 24th October, 1940; and Ernest Brougham Docker, 31st October, 1940.

Captain W. J. Binns, M.C., is placed on the Retired List with permission to retain his rank.

Honorary Lieutenant-Colonel S. A. Smith and Honorary Captains J. Coen and W. Mawson are retired.

To be Honorary Major.—Honorary Captain W. L. Calov, 22nd October, 1940. *To be Honorary Captains.*—Clement Maurice Ryan, 19th August, 1940; Robert Fergus Back, Russell William Richards and Francis Patrick Ryan, 23rd October, 1940; Richmond Jeremy, 26th October, 1940; Laurence Alan Moxham, 30th October, 1940; James Tatham Jefferis, Joseph Gregory Buckley and Ian Douglas Miller, 31st October, 1940; Henry Houghton Burton Bradley and Terence Kingsmill Abbott, 8th November, 1940; and Mure Royston Robertson, 13th November, 1940.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

Honorary Captain C. M. Greer is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), 2nd October, 1940.

The provisional appointment of Captain O. B. Goyen is terminated, 2nd October, 1940.

To be Major (temporarily).—Captain (provisionally) C. W. Ross, 21st September, 1940.

To be Major (temporarily).—Captain A. R. Buchanan, 6th October, 1940.

To be Captain (provisionally).—Albert Ezekiel Leffers, 24th October, 1940.

Honorary Captain H. L. Andrews is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), 23rd October, 1940, and to be Major (temporarily), 24th October, 1940.

Honorary Captain F. M. Blackall is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), 1st November, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains.—George Franklyn Russell Cole, 3rd October, 1940; John Joseph Laing, 4th October, 1940; Lucy Meredith Bryce, Colin Campbell Reid, Henry Shannon, Frank Conrad Hope Ross, Douglas Harold Mitchell and Francis Herbert Jackson, 19th October, 1940; Kenneth Francis O'Donnell and Howard Ernest Williams, 20th October, 1940.

The resignation of Captain G. Simpson of his commission is accepted, 21st October, 1940.

The resignation of Honorary Captain T. G. Millar of his commission is accepted, 6th November, 1940.

To be Honorary Captains.—James Wilson Cook, Bernard Bretton-Watson and Nelson Norrie Harrington, 14th November, 1940.

Award of the Australian Efficiency Decoration: Australian Army Medical Corps.

Colonel A. P. Derham, M.C.

Fourth Military District.

Australian Army Medical Corps.

To be Captain (provisionally).—Guy Austin Lendon, 26th September, 1940.

To be Captain (provisionally).—Richard De Garis Burnard, 26th June, 1940.

The resignation of Captain (provisionally) H. D. Sutherland of his commission is accepted, 8th November, 1940.

Honorary Captain G. E. Jose is appointed from the Reserve of Officers (A.A.M.C.), and to be Captain (provisionally), 23rd September, 1940, and to be Major (temporarily), 24th September, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captain.—Albert Edward Platt, 24th October, 1940.

Major J. W. Flood is transferred to the Reserve of Officers (A.A.M.C.), 8th Military District.

Major W. J. E. Phillips, Captain R. W. Hogg and Honorary Captains F. F. Coffey and H. A. Faulkner are retired.

To be Honorary Captains.—Howard John Edelman, 11th October, 1940; Walter Raymond Phillips, 20th October, 1940, and William Gordon Heaslip, 5th November, 1940.

Sixth Military District.

Australian Army Medical Corps Reserve.

To be Honorary Major.—Douglas William Leigh Parker, 14th September, 1940.

To be Honorary Captains.—Keith Daubert Anderson, 21st September, 1940, and Geoffrey Herbert Wymond, George Thomas Hamlyn Harris and Harry Kelly, 12th October, 1940.

WESTERN COMMAND.

Fifth Military District.

Australian Army Medical Corps.

To be Major (temporarily).—Captain O. R. Corr, 21st November, 1940.

Captain C. E. Cook is appointed from the Reserve of Officers (A.A.M.C.), and to be Major (temporarily), 25th October, 1940.

Australian Army Medical Corps Reserve.

To be Honorary Captains.—Harold William Wakefield Roy Kent and Marion Aroha Redcliffe-Taylor, 15th October, 1940.

To be Honorary Captains.—Vernon Allan Fergusson Stewart and John Halliday Coto, 1st November, 1940.

Seventh Military District.

Australian Army Medical Corps.

Honorary Captain W. T. J. Harris is appointed from the Reserve of Officers (A.A.M.C.), 2nd Military District, and to be Captain (provisionally), 14th November, 1940.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force—Medical Branch.

The probationary appointments of the following flight lieutenants are confirmed: R. C. Angove, S. B. Forgan, and E. W. Field.

Flight Lieutenant A. A. Green is granted the acting rank of Squadron Leader, with effect from 1st October, 1940.

The following are granted commissions on probation with the rank of Flight Lieutenant and the temporary rank of Squadron Leader with effect from 16th November, 1940: Leslie Everton Hurley, M.D., M.S., F.R.A.C.P., John O'Sullivan, M.D., B.S., F.R.A.C.P., F.F.R., D.M.R.E., Harold William Saville, M.B., B.S., D.L.O., F.R.A.C.S., and Neville Graham Sutton, M.B., Ch.M., F.R.C.S.

The following Flight Lieutenants are transferred from the Reserve to the Active List, and are granted the temporary rank of Squadron Leader with effect from 1st December, 1940: (Honorary Squadron Leader) J. H. B. Brown, M.B., Ch.B., (Honorary Squadron Leader) A. T. Roberts, M.B., Ch.M., F.R.C.S., and H. G. Allen, M.B., Ch.M., F.R.A.C.S.

The following are granted commissions on probation with the rank of Flight Lieutenant with effect from 18th November, 1940: Thomas Bruce Lindsay, B.D.S., and Thomas Graham Thorpe, B.D.S.

Clifford Henry Coomer Searby, B.Sc., M.B., M.S., F.R.C.S., F.R.A.C.S., is granted a commission on probation with the rank of Flight Lieutenant and the temporary rank of Squadron Leader, with effect from 18th November, 1940.

The probationary appointments of the following Flight Lieutenants are confirmed: G. S. Colvin, R. G. Johnston and J. E. Jordan.

The probationary appointments of the following Flight Lieutenants are confirmed: B. P. K. Ryan, F. S. Parle, J. A. Game, R. C. Angove, W. A. Seldon, J. M. Rainbow, I. L. Miller, J. G. Radford, E. L. Davey, S. B. Forgan, J. D. Russell, J. L. R. Carter, C. P. Hudson, H. D. Phipps, J. F. Frayne, K. E. Rex, E. W. Field, R. G. Plummer, R. J. Stabback, H. A. Sunstrup and A. S. De B. Cocks.—(Ex. Min. No. 92—Approved 11th December, 1940.)

Reserve—Medical Branch.

Flight Lieutenant R. G. Weaver is transferred to the Reserve, with effect from 6th November, 1940.

Flight Lieutenant H. J. Edelman relinquishes his commission, with effect from 23rd October, 1940.—(Ex. Min. No. 89—Approved 11th December, 1940.)

The following are granted commissions on probation with the rank of Flight Lieutenant with effect from 25th November, 1940: Thomas Glass Millar, M.B., B.S., F.R.C.S., D.L.O., F.R.A.C.S., George Bentham Morris, M.B., B.S., and George Simpson, M.B., B.S., M.R.C.P., D.G.O., M.R.C.O.G.—(Ex. Min. No. 90—Approved 11th December, 1940.)

The following are granted commissions on probation with the rank of Flight Lieutenant, with effect from 18th November, 1940: Bruce Carlyle Pirie, M.B., B.S., and Sidney Fergus McRae Yeates, M.B.—(Ex. Min. No. 91—Approved 11th December, 1940.)

Correspondence.

THE USE OF HISTAMINE IN THE TREATMENT OF NEURO-VASCULAR HEADACHE.

SIR: In your number of December 7, 1940, Dr. Reid, in reply to my letter concerning his paper on "Treatment of Neuro-Vascular Headache by Injection of Histamine", has acknowledged that headache may be due to allergy, but indicates that the cases he treated were not of this nature; however, he now agrees that allergy should be considered and, if discovered, treated before a patient is subjected to the histamine treatment.

Therefore it seems necessary for me to again emphasize the fact that just such cases as those mentioned in his article are very frequently allergic and should be treated accordingly. Although Dr. Reid now suggests that he emphasized the necessity of excluding pathological lesions (including allergy), no mention was made of this subject in his paper, and in fact it would be interesting to hear what steps were taken in the cases mentioned to exclude allergy as a factor. Some details of tests made would be appreciated.

The term "neuro-vascular" reminds us that many allergic manifestations are brought about through effects on the blood vessels of the part concerned.

Yours, etc.,

D. L. BARLOW.

North Terrace,
Adelaide,
December 13, 1940.

ACUTE ABDOMINAL CONDITIONS IN CHILDREN.

SIR: Kindly allow me to direct attention to the subject matter, acute appendicitis, appearing in Dr. Hipsley's very interesting article in your issue under date December 21, 1940.

The writer points out in no uncertain manner the absence of muscular rigidity in deep pelvic appendicitis, which is often responsible for the delay of several days in making a diagnosis.

The young irritable refractory type of child does not permit of an informative examination while resentful and bellicose.

It is obvious that the doctor has assumed that we all should know how to overcome this difficulty, but I fear that many do not.

One should aim in producing an extremely light stage of anaesthesia, sufficient to quieten the child, but not so deep as to abolish its response to painful stimuli which can be elicited by abdomino-rectal examination.

There are two other important clinical signs not so generally known, one, a ballooning of the rectum, and another, vague urinary disturbances unexplained by urinalysis; both due perhaps to disturbance of the parasympathetic.

To these may be added a white cell count, and the persistent greyish white tongue, which clears but little during the course of the illness.

Dr. Hipsley's statement that the Ochsner-Sherren treatment has no place in the treatment of acute appendicitis in children is quite justifiable, on histological grounds alone.

Yours, etc.,

W. W. CAMERON.

Short Street,
Mudgee,
New South Wales.
December 20, 1940.

SO-CALLED REFLEX ANURIA.

SIR: Dr. Hipsley's article on "so-called reflex anuria" (THE MEDICAL JOURNAL OF AUSTRALIA, December 7, 1940) must be of interest to all practising surgeons, as it deals with one of the unpredictable complications of operations. Although

I am in complete agreement with him that the term "reflex" is almost certainly a misnomer in this type of case, some of his observations call for contrary comment.

1. He states that "the symptoms recorded in all cases are similar to those commonly seen in renal colic due to stone". In the four such cases which have come under my notice (one of which is quoted by Dr. Hipsley) this was not so. There is every sign of obstruction to the upper urinary tract but an entire absence of the typical colicky pain.

2. With reference to "radio-lucent" calculi may I also quote Swift Joly ("Stone and Calculous Diseases of the Urinary Organs", page 315): "I believe it is possible to determine the position and shape of all stones of more than 2 or 3 mm. diameter, providing they are not composed of pure uric acid."

In the case cited by Dr. Hipsley, in which he removed "three uric acid calculi, each as large as a pea", there should have been no difficulty in demonstrating the stone by pyelography.

3. A propos of the next case cited, Dr. Hipsley omits to mention whether the upper part of the ureter was distended with urine as well as the renal pelvis.

In calculous anuria and other simple mechanical ureteric obstructions this condition is invariably found.

In three such cases in which I have exposed the kidney, the ureter has not been distended, and in the sole post-mortem specimen examined the ureteric lumen was entirely occupied by oedematous mucosa and submucosa. In these cases all urine is strained through fine mesh gauze, but no calculus has yet been recovered.

On these experiences I cannot concur that these cases are all due to calculi, and it would indeed be a strange coincidence if 70% of cases with calculous anuria had undergone operation a few days previously, as his cases suggest.

A possible explanation of the post-operative cases lies in the dehydration and toxæmia (anaesthetic and focal) which sometimes accompanies operation, but I can offer no suggestion as to why ureteric catheterization is so often prevented by oedema.

Yours, etc.,

COLIN EDWARDS.

British Medical Association House,
137, Macquarie Street,
Sydney.
December 20, 1940.

Honours.

NEW YEAR HONOURS.

HIS MAJESTY THE KING has been pleased to confer the following honours on medical practitioners in Australia:

Knight Bachelor: Dr. Constantine Trent Champion de Crespigny, D.S.O., of Adelaide.

Companion of the Most Distinguished Order of Saint Michael and Saint George: Dr. Bernard Traugott Zwar, of Melbourne.

Commander of the Most Excellent Order of the British Empire: Dr. Thomas Herbert Goddard, of Hobart.

Officer of the Most Excellent Order of the British Empire: Dr. Clyde Cornwall Fenton, of Katherine, Northern Australia; Dr. Katie Ardill-Brice, of Sydney; Dr. Arthur Aubrey Palmer, of Sydney.

The congratulations of the medical profession are offered to these recipients.

Australian Medical Board Proceedings.

QUEENSLAND.

THE undermentioned have been registered, pursuant to the provisions of *The Medical Act of 1939*, of Queensland, as duly qualified medical practitioners:

Grainger, Francis Transvaal, M.B., Ch.M., 1925 (Univ. Sydney), Oxford House, Ann Street, Brisbane.

Turner, James Ronald, M.B., Ch.B., 1937 (Univ. New Zealand), c/o Dr. N. M. Gutteridge, Gympie Road, Kedron.

SOUTH AUSTRALIA.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Practitioners Act, 1919 to 1935*, of South Australia, as duly qualified medical practitioners:

- Le Messurier, David Hugh, M.B., Ch.B., 1940 (Edinburgh), Adelaide Hospital, Adelaide.
 Verco, Luke Everard, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Wallman, Leigh Stuart, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Oldfield, Neil, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Silms, Eric Baldwin, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Smith, William Arthur Rushbrook, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Nichterlein, Otto Erhardt, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Holmes, Henry Bertram, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Hains, Robert Myer, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Ryan, Naomi Rosslyn, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Semler, Clifford Gerhardt, M.B., B.S., 1940 (Univ. Adelaide), Adelaide Hospital, Adelaide.
 Stephens, Willem Lodewyk Bosschart, M.B., B.S., 1929 (Univ. Melbourne), Royal Australian Air Force.

The following additional qualifications have been registered:

- Naylor, Rupert Leslie, Melbourne (M.B., B.S., 1924, Univ. Adelaide), D.O.M.S., London, 1940.
 Binns, Raymond Thomas, 2/8 Field Ambulance, Australian Imperial Force (M.B., B.S., 1923, Univ. Adelaide), M.R.A.C.P., 1940.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

- Corlis, Geoffrey Charles, M.B., B.S., 1940 (Univ. Sydney), Saint Vincent's Hospital, Darlinghurst.

The undermentioned has applied for election as a member of the Western Australian Branch of the British Medical Association:

- Musso, Louis Albert Maria Bellotti, M.B., B.S., 1937 (Univ. Sydney), Derby.

Medical Appointments.

Dr. C. A. Finlayson and Dr. J. S. Proctor have been appointed Official Visitors to the Mental Hospital at Parkside, South Australia, pursuant to the provisions of the *Mental Defectives Act, 1935-1939*.

Dr. W. L. B. Stephens has been appointed Temporary Honorary Clinical Assistant to the Surgical Section of the Royal Adelaide Hospital, Adelaide.

Dr. C. P. O'Toole has been appointed Medical Inspector of Seamen at Wyndham, Western Australia, in accordance with the provisions of the *Navigation Act, 1912-1935*.

Books Received.

"Infant Feeding", by A. Moncrieff, M.D., F.R.C.P.; 1940. London: Edward Arnold and Company Limited. Demy 8vo, pp. 34. Price: 1s. 6d. net.

"Lectures on Diseases of Children", by R. Hutchison, Bt., M.D., LL.D., F.R.C.P., and A. Moncrieff, M.D., F.R.C.P.; Eighth Edition; 1940. London: Edward Arnold and Company. Demy 8vo, pp. 479, with illustrations. Price: 21s. net.

"The Early Treatment of Nervous and Mental Disorders", by W. L. Neustatter, B.Sc., M.B., B.S., M.R.C.P.; 1940. London: J. and A. Churchill. Demy 8vo, pp. 391. Price: 15s. net.

"Venereal Diseases", by E. T. Burke, D.S.O., M.B., Ch.B.; 1940. London: H. K. Lewis and Company Limited. Demy 8vo, pp. 566, with 133 illustrations and 6 coloured plates. Price: 30s. net.

"Injuries of the Jaws and Face, with Special Reference to War Casualties", by W. W. James, O.B.E., F.R.C.S., LL.D.S., and B. W. Pickling, F.R.C.S., LL.D.S.; 1940. London: John Bale and Staples Limited. Medium 8vo, pp. 206, with 194 illustrations. Price: 15s. net.

"Mosquito Control, Practical Methods for Abatement of Disease Vectors and Pests", by W. B. Herms, Sc.D., and H. F. Gray, Gr.P.H.; 1940. London: Oxford University Press. Super royal 8vo, pp. 329, with illustrations. Price: 20s. net.

Diary for the Month.

- JAN. 14.—Tasmanian Branch, B.M.A.: Branch.
 JAN. 22.—Victorian Branch, B.M.A.: Council.
 JAN. 24.—Queensland Branch, B.M.A.: Council.
 JAN. 31.—Tasmanian Branch, B.M.A.: Council.
 FEB. 4.—New South Wales Branch, B.M.A.: Organization and Science Committee.
 FEB. 5.—Western Australian Branch, B.M.A.: Council.
 FEB. 5.—Victorian Branch, B.M.A.: Branch.
 FEB. 6.—South Australian Branch, B.M.A.: Council.
 FEB. 7.—Queensland Branch, B.M.A.: Branch.
 FEB. 11.—Tasmanian Branch, B.M.A.: Branch.
 FEB. 11.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmalm United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phoenix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

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